UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: 04/08/2015

SUBJECT: Fluopyram: Executive summaries for the global reviews on 32 toxicity studies

PC Code: 080302
Decision No.: NA
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0054868
MRID No.: (47372441 to 47372523)

DP Barcode: D353273
Registration No.: NA
Regulatory Action: NA
Case No.:
CAS Nos. 658066-35-4
40 CFR: § 180.661

FROM: Whang Phang, Toxicologist
Risk Assessment Branch III (RAB3)
Health Effects Division (HED) (7509P)
Office of Pesticide Programs (OPP)

THRU: Christine Olinger, Branch Chief
Risk Assessment Branch III
HED/OPP (7509P)

TO: IHAD Record
HED

Fluopyram was a global review chemical, and EU was the lead reviewer for toxicology. The toxicology reviews were written according to the OECD format; HED generated the executive summary according the HED format for each study. The MRID number for each study is presented below and the DER for the executive summaries are attached.

47372441	47372442	47372443	47372444	47372445
47372446	47372447	47372448	47372449	47372450
47372501	47372502	47372503	47372504	47372505
47372506	47372507	47372508	47372509	47372510
47372511	47372512	47372513	47372514	47372515
47372516	47372517	47372518	47372519	47372520
47372521	47372522	47372523		

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: OPPTS 870.3100; '82-1a, Subchronic Oral Toxicity Study in Rats

Work Assignment No. 6-1-229 D (MRID 47372441)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Building 100, Suite B
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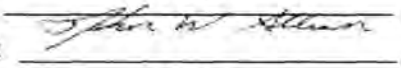
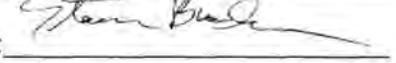
Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature:  Date: *11/10/09*
Secondary Reviewer: John W. Allran, M.S.	Signature:  Date: *11/10/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature:  Date: *11/10/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature:  Date: *11/10/09*

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EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/23/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Lori Brunsman
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/'11

DATA EVALUATION RECORD

STUDY TYPES: Subchronic Oral (Diet) Toxicity Study in Rats; OPPTS 870.3100 [' 82-1a]; OECD 408.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0054868

TEST MATERIAL (PURITY): Fluopyram (99.0%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Kennel, P. (2005) AE C656948: 90-day toxicity study in the rat by dietary administration. Bayer CropScience, Sophia Antipolis Cedex, France. Laboratory Report Nos.: SA 04048, M-250946-01, ASB2008-5548, May 10, 2005. MRID 47372441. Unpublished

SPONSOR: Bayer CropScience, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 47372441), fluopyram (99.0% a.i., Lot/Batch PFI 0304) was administered in the diet to ten Wistar (Rj:WI [IOPS HAN]) rats/sex/dose group at dose levels of 0, 50, 200, 1000, or 3200 ppm (equivalent to 0/0, 3.06/3.63, 12.5/14.6, 60.5/70.1, and 204/230 mg/kg/day in males/females) for at least 90 days. Additionally, groups of ten rats/sex/dose group were administered the test substance in the diet at dose levels of 0 or 3200 ppm for at least 90 days and then maintained on basal diet for a minimum of 28 days to examine the reversibility of any treatment-related effects. In addition to the customary parameters, animals of the main treatment group were assessed for neurotoxicity on Study Weeks 11 and 12 by observers who were "blind" to the dose groups of the animals. Motor activity, sensor reactivity, and grip strength were recorded. Additionally, during Weeks 3 and 13 of the treatment period, and Week 5 of the recovery period, blood samples were collected and T3, T4, and TSH levels were measured.

There were no effects of treatment observed on clinical signs, motor activity, sensor reactivity, grip strength, or ophthalmoscopic examinations.

There were no treatment-related deaths. One 1000 ppm male was euthanized on Day 37 having had a distended abdomen between Days 22 and 37 and general pallor between Days 27 and 37. This animal was noted to have a pale appearance and an enlarged, irregular, and red mottled liver

at necropsy; a cause of death was not reported. One 50 ppm male was killed on Day 57 having been noted to have labored and noisy respiration, a wasted appearance, piloerection, and ocular discharge from both eyes on the day of termination, together with a body weight loss of 8.2 g/day and reduced food consumption during the week prior to sacrifice. The condition of this animal was attributed to accidental trauma, as soiled fur around both eyes and a fracture of the nasal cavity were discovered at necropsy. All other animals survived to scheduled termination.

At 3200 ppm, the **liver** toxicity findings observed at 1000 ppm were increased in severity and magnitude and more frequently noted in both sexes. In addition to the findings in the liver noted above, triglycerides were increased in the females and higher mean prothrombin times were noted in the males. In the **thyroid**, absolute and relative weights were increased in both sexes, with minimal to slight diffuse follicular cell hypertrophy noted in the majority (8/10) of the males; minimal diffuse follicular cell hypertrophy was noted in one female. TSH was increased in both sexes at Week 3, and in the males at Week 13. T3 was increased in the females at Week 3, and in the males at Week 13. T4 was increased in the females at Week 3. Additionally at this dose, body weights were slightly decreased throughout the study, resulting in a decrease in overall body weight gains in both sexes. Food consumption was slightly decreased from Day 29-90 in the females.

Treatment-related **liver** toxicity was observed at 1000 ppm. Absolute and relative (to body) liver weights were increased by 20-27% in both sexes. Total cholesterol was increased by 45-48% in both sexes, and gamma glutamyltransferase was increased by 480% in the females. At necropsy, obviously large liver was observed in 6/9 males and 7/10 females, dark liver was noted in 2/9 males, and prominent liver lobulation was observed in 4/9 males. Minimal to slight diffuse centrilobular hepatocellular hypertrophy was noted in 9/9 males and 7/10 females, and minimal focal/multifocal periportal to midzonal hepatocellular macrovacuolation was observed in 6/10 females. Additionally at 1000 ppm, minimal to slight diffuse follicular cell hypertrophy was noted in 4/9 males and 2/10 females, and TSH and T4 were increased by 54% and 43%, respectively, in the males.

At 200 ppm, certain effects (such as increased total cholesterol, increased gamma glutamyltransferase in the females only, increased liver weigh (5-11%). enlarged liver, minimal diffuse centrilobular hepatocellular hypertrophy, minimal focal/multifocal periportal to midzonal hepatocellular macrovacuolation) were found in a small number of test animals. The severity and magnitude of effect were minimal relative to the effects seen in 1000 ppm group. These minor findings were considered to represent an adaptive response of the liver to exposure to the test compound and were not considered adverse.

Kidney toxicity was noted in the males at 1000 ppm and above. Absolute and relative kidney weights were increased by 25-34%. Obviously large kidney and pale kidney were noted in the majority of the 1000 ppm and above males at necropsy, and in 1-3 males at 50 and 200 ppm. The increased weights were associated with microscopic changes of hyaline droplet nephropathy (hyaline droplets in the proximal tubule, focal/multifocal basophilic tubules, granular casts in the medulla, and focal/multifocal hyaline casts) observed in all dose groups, increasing in severity and frequency with increasing dose. Cellular casts in the urine were also noted at all dose levels

in the males. This nephropathy was considered to be due to accumulation of $\alpha_{2\mu}$-globulin, a common toxicological finding in young male rats following exposure to toxicants. Therefore, these findings were not considered relevant to human health considerations.

During the recovery period, there was a tendency towards reversibility in the majority of the animals treated with 3200 ppm of the test compound. The findings in the male kidney tended to be the most persistent.

The LOAEL is 1000 ppm (equivalent to 60.5/70.1 mg/kg/day in males/females), based on liver toxicity as described above and diffuse follicular cell hypertrophy in both sexes, and increased TSH and T4 in the males. The NOAEL is 200 ppm (equivalent to 12.5/14.6 mg/kg/day in males/females).

This study is considered **acceptable/guideline** and satisfies the requirements (OPPTS 870.3100; OECD 408) for a subchronic toxicity study in rodents.

COMPLIANCE: As only a summary of the study was provided for review, it is not known if compliance documents were provided. It was stated that the study did meet GLP Compliance standards.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: OPPTS 870.3100; '82-1a, Subchronic Oral Toxicity Study in Mice

Work Assignment No. 6-1-229 E (MRID 47372442)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
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Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/10/09*
Secondary Reviewer: John W. Allran, M.S.	Signature: John W Allran Date: *11/10/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/10/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Steven Brecher Date: *11/10/09*

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EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/23/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Lori Brunsman
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPES: Subchronic Oral (Diet) Toxicity Study in Mice; OPPTS 870.3100 ['82-1a]; OECD 408.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (99.0%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Kennel, P. (2005) AE C656948: 90-day toxicity study in the mouse by dietary administration. Bayer CropScience, Sophia Antipolis Cedex. Laboratory Report Nos.: SA 04052, M-251136-01, ASB2008-5549, May 12, 2005.MRID 47372442. Unpublished

SPONSOR: Bayer CropScience, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 47372442), fluopyram (99.0% a.i., Lot/Batch PFI 0304) was administered in the diet to ten C57BL/6J mice/sex/dose group at dose levels of 0, 30, 150, or 1000 ppm (equivalent to 0/0, 5.4/6.8, 26.6/32.0, and 188/216 mg/kg/day in males/females) for at least 90 days.

There were no effects of treatment observed on clinical signs, body weights, body weight gains, or food consumption.

There were no treatment-related deaths. One 30 ppm male was found dead on Day 30 after a body weight loss of 6.9 g between Days 15-29 and reduced food consumption between Days 9-29. Clinical signs included reduced motor activity on Days 22-23 together with wasted appearance and hunched posture during Days 22-29. Spontaneous hydrocephalus was observed at necropsy and confirmed microscopically. This was considered to be the cause of death for this animal. One control male was killed for humane reasons on Day 69 after an accidental trauma. All other mice survived to scheduled termination.

Treatment-related **liver** toxicity was observed at 1000 ppm. Alanine aminotransferase was increased by 109-205% in both sexes, and alkaline phosphatase and aspartate aminotransferase were increased by 21% and 46%, respectively, in males. Absolute and relative (to body) liver

weights were increased by 36-45% in both sexes, corresponding to enlarged liver in 8/10 males and 9/10 females. Dark liver was noted in 5/10 males and 10/10 females. Microscopically, centrilobular hepatocellular hypertrophy was observed in 10/10 males (moderate severity) and 10/10 females (minimal to moderate severity). Focal necrosis was noted in 3/10 males (minimal severity) and 6/10 females (minimal to slight severity).

Additionally at 1000 ppm, absolute and relative adrenal gland weights were increased by 87-92% in the males. Microscopically in the adrenal glands, there was a lower incidence of cortical ceroid pigment in the males, and a greater incidence of minimal to slight cortical vacuolation in the females.

At 150 ppm, absolute and relative liver weights were increased by 14-28% in both sexes. Centrilobular hepatocellular hypertrophy was observed in 10/10 males (minimal to slight severity) and 5/10 females (minimal severity). These minor findings were considered to represent an **adaptive** response of the liver to exposure to the test compound and were not considered adverse.

The LOAEL is 1000 ppm (equivalent to 188/216 mg/kg/day in males/females), based on liver toxicity as described above in both sexes, increased adrenal gland weights and lower incidence of adrenal gland cortical ceroid pigment in males, and a greater incidence of cortical vacuolation of the adrenal gland in females. The NOAEL is 150 ppm (equivalent to 26.6/32.0 mg/kg/day in males/females).

This study is considered **acceptable/guideline** and satisfies the requirements (OPPTS 870.3100; OECD 408) for a subchronic toxicity study in rodents.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality Statements were included in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: OPPTS 870.3150; '82-1b, Subchronic Oral Toxicity Study in Dogs

Work Assignment No. 6-1-229 F (MRID 47372443)

Prepared for
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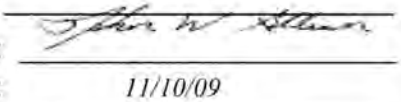
Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature:  Date: *11/10/09*
Secondary Reviewer: John W. Allran, M.S.	Signature:  Date: *11/10/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature:  Date: *11/10/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature:  Date: *11/10/09*

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EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/23/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Lori Brunsman
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPES: Subchronic Oral (Diet) Toxicity Study in Dogs; OPPTS 870.3150 ['82-1b]; OECD 409.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.6%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Kennel, P. (2006) AE C656948: 90-day toxicity study in the dog by dietary administration. Bayer CropScience, Sophia Antipolis Cedex, France. Laboratory Report Nos.: SA 05046, M-276047-01, ASB2008-5550; August 17, 2006. MRID 47372443. Unpublished

SPONSOR: Bayer CropScience, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 47372443), fluopyram (94.6% a.i., Batch 08528/0002) was administered in the diet to four beagle dogs/sex/dose group at dose levels of 0, 800, 5000, or 20,000 ppm (equivalent to 0/0, 28.5/32.9, 171/184, and 332/337 mg/kg/day in males/females) for at least 90 days. The highest dietary concentration was reduced to 10,000 ppm on Day 15 due to body weight losses and decreased food consumption during the first two weeks, which were attributed to a lack of palatability of the test substance in the diet.

There were no effects of treatment observed on mortality, during the ophthalmoscopic examinations, or on urinalysis. All dogs survived to scheduled euthanasia.

Treatment-related **liver** toxicity was observed at 5000 ppm. Absolute and relative (to body) liver weights were increased by 59-69% in the males and by 35-49% in the females. The following changes in clinical chemistry parameters were observed in both sexes at Weeks 8 and 13: (i) alkaline phosphatase was increased by 169-300%; (ii) gamma glutamyltransferase was increased by 50-200%; (iii) albumin was decreased by 17-22%; and (iv) albumin/globulin ratio was decreased by 21-34%. The changes generally increased in magnitude with time. At necropsy, enlarged liver was noted in 1/4 males and females. The following microscopic findings were noted in the liver (all compared to 0 controls): (i) minimal to slight diffuse hepatocellular hypertrophy in 4/4 males and females; (ii) multifocal intracytoplasmic eosinophilic droplets in

3/4 males (minimal to slight severity) and 4/4 females (minimal to moderate severity); and (iii) focal/multifocal hepatocellular single cell necrosis in 2/4 males (minimal severity).

Additionally at 5000 ppm, overall (Weeks 1-13) food consumption was decreased by 7% in males and by 22% in females. This decrease was also attributed to a lack of palatability of the dietary formulations. Thymic involution (decreased size of cortex) was increased in severity (minimal to slight) in all males and females compared to controls (minimal); however, this finding was considered to be secondary to the decreased food consumption.

At 20,000/10,000 ppm, the findings observed at 5000 ppm were increased in severity and magnitude and more frequently noted in both sexes. In addition to the findings in the liver noted above, increases in aspartate aminotransferase (incr. 54-75%) and alanine aminotransferase (incr. 259-594%) were noted in the males at Weeks 8 and 13. Additional findings of toxicity included a wasted appearance noted for one male and two females. This observation was noted in correlation with body weight loss and corresponding marked reduction in food consumption in both sexes during Weeks 1 and 2. These findings were attributed to a lack of palatability of the test diets at this concentration. Overall (Weeks 1-13) body weight losses of 0.8 kg in males and 1.1 kg in females were noted (compared to gains of 1.0 kg in controls), corresponding to decreases in overall food consumption of 25% and 46% in males and females, respectively. Platelet counts were increased by 30-56% in both sexes during Weeks 8 and 13.

Also at 20,000/10,000 ppm, absolute and relative thymus weights were decreased by 61-71% in the females, and 4/4 females were in anestrus compared to 1/4 controls. These findings were considered to be secondary to the reductions in body weight gains and food consumption.

At 800 ppm, absolute and relative liver weights were increased by 25-39% in both sexes. This finding was considered to represent an **adaptive** response of the liver to exposure to the test compound, and was not considered adverse.

The LOAEL is 5000 ppm (equivalent to 171/184 mg/kg/day in males/females), based on liver toxicity as described above in both sexes. The NOAEL is 800 ppm (equivalent to 28.5/32.9 mg/kg/day in males/females).

This study is considered **acceptable/guideline** and satisfies the requirements (OPPTS 870.3150; OECD 409) for a subchronic toxicity study in dogs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality Statements were included in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: OPPTS 870.3200; '82-2, 28-Day Dermal Toxicity Study in Rats

Work Assignment No. 6-1-229 G (MRID 47372444)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
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Prepared by
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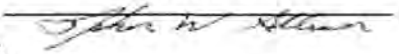
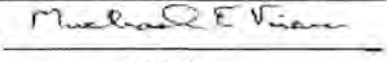
Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature:  Date: *11/10/09*
Secondary Reviewer: John W. Allran, M.S.	Signature:  Date: *11/10/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature:  Date: *11/10/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature:  Date: *11/10/09*

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EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Lori Brunsman
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/'11
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPES: 28-Day Dermal Toxicity Study in Rats; OPPTS 870.3200 ['82-2]; OECD 410.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.7%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Eigenberg, D.A. (2007) A subacute dermal toxicity study in rats with technical grade AE C656948. Bayer CropScience LP, Stilwell, Kansas. Study No. 06-S22-GH; Report No.: 201617; M-293833-01, ASB2008-5551, Oct. 16, 2007. MRID 47372444. Unpublished

SPONSOR: Bayer CropScience, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a 28-day dermal toxicity study (MRID 47372444), fluopyram (94.7% a.i., Batch 08528/0002) was applied to the shaved (intact) dorsal and lateral skin of ten Wistar rats/sex/dose group at dose levels of 0, 100, 300, and 1000 mg/kg/day for a minimum of six hours/day, five consecutive days/week, for four weeks.

There were no effects of treatment observed on mortality, clinical signs, body weights, food consumption, or gross pathology.

At 1000 mg/kg/day, treatment-related effects were observed on the **liver**. Relative (to body) liver weights were increased in the males, and absolute and relative liver weights were increased in the females. Microscopically, increased incidence of centrilobular and mid-zonal hypertrophy were observed in the liver of males and females. Additionally, prothrombin time was increased in the males, and total cholesterol was increased in the females.

The LOAEL for systemic toxicity is 1000 mg/kg/day, based on liver toxicity as described above. The NOAEL is 300 mg/kg/day.

There were no local effects observed on the skin at any dose level.

The LOAEL for dermal toxicity was not observed. The NOAEL is 1000 mg/kg/day.

This study is considered **acceptable/guideline** and satisfies the requirements (OPPTS 870.3200; OECD 410) for a 28-day dermal toxicity study in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality Statements were included in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: OPPTS 870.3700a [§83-3a]; Developmental Toxicity Study in Rats

Work Assignment No. 6-01-229 K (MRID 47372445)

Prepared for
Health Effects Division
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2777 South Crystal Drive
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Signature: David A McEwen
Date: 11/30/09

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Michael E. Viana, Ph.D., D.A.B.T.
Signature: Michael E Viana
Date: 11/30/09

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.
Signature: Michael E Viana
Date: 11/30/09

Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T.
Signature: Steven Brecher
Date: 11/30/09

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EPA Reviewer: Whang Phang **Signature:** [signature]
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
EPA Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** [signature]
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11
Template version 02/06

STUDY TYPE: Prenatal Developmental Toxicity Study in Rats (gavage); OPPTS 870.3700a ['83-3a]; OECD 414.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.6% a.i.; Lot/Batch # 08528/0002)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948;

CITATION: Wason, S. (2008) AE C656948: Developmental toxicity study in the rat by gavage. Bayer CropScience, Sophia Antipolis, France. Laboratory Project Nos. SA 05276, M-299438-01, ASB2008-5481. March 31, 2008. MRID 47372445. Unpublished.

SPONSOR: Bayer CropScience

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 47372445), AE C656948 (Fluopyram, 94.6% a.i.; Lot/Batch # 08528/0002) in 0.5% aqueous methylcellulose 400 was administered via daily oral gavage in a dose volume of 10 mL/kg to 23 time-mated Sprague-Dawley rats/dose group at doses of 0, 30, 150, or 450 mg/kg/day from gestation days (GD) 6-20. On GD 21, all dams were euthanized; each dam's uterus was removed via cesarean section and its contents examined. Fetuses were examined for external, visceral, and skeletal malformations and variations.

No compound-related effects were observed on mortality, clinical signs of toxicity, or pregnancy rate.

At 450 mg/kg/day, maternal body weight gain was decreased ($p<0.01$) by 16% during GD 6-21, and food consumption was decreased by 13-15% at all intervals from GD 6-14. Liver weights were increased ($p<0.01$) by 40% compared to controls and enlarged liver was also noted grossly in 4/23 females at this dose (vs. 0/23 controls). Microscopic findings were limited to slight to marked diffuse centrilobular hepatocellular hypertrophy in all treated females at this dose (vs. 0/23 controls).

At 150 mg/kg/day, maternal body weight gain was decreased by 6% during GD 6-21, and food consumption was decreased by 10-18% at all intervals from GD 6-14. Liver weights were increased ($p<0.01$) by 15% compared to controls. Microscopic findings were limited to minimal

to moderate diffuse centrilobular hepatocellular hypertrophy in 20/23 females at this dose (vs. 0/23 controls).

At 30 mg/kg/day, food consumption was decreased ($p<0.01$) by 10% on GD 6-8; however, overall (GD 6-21) body weight gains were similar to controls.

The maternal LOAEL is 150 mg/kg/day based on decreased body weight gains and food consumption, and liver effects (increased liver weights and incidence of diffuse centrilobular hepatocellular hypertrophy). The maternal NOAEL is 30 mg/kg/day.

There were no treatment-related effects on abortions, premature deliveries, complete litter resorptions, or dead fetuses and no effects of treatment on the numbers of litters, live fetuses, early resorptions, or late resorptions. There were no treatment-related external, visceral, or skeletal malformations, and no external variations.

At 450 mg/kg/day, mean fetal body weight was decreased ($p<0.05$) by 5% for both the combined and separate sexes. The incidence of the visceral variations "thymic remnant present (unilateral/bilateral)" and "ureter (unilateral/bilateral); convoluted and /or dilated" was higher at the fetal and/or litter level than in the control group, and was outside the historical control range for both parameters. Additionally, there was a higher incidence of the skeletal variations "at least one thoracic centrum split/split cartilage" and "at least one thoracic centrum: dumbbell and/or bipartite/normal cartilage", compared with the control group. The incidence was outside the historical control range at both the fetal and litter level for both findings.

The developmental LOAEL was 450 mg/kg/day based on decreased fetal body weights, and increased incidence of visceral and skeletal variations. The developmental NOAEL is 150 mg/kg/day.

This study is classified **acceptable/guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality Statements were included in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: OPPTS 870.3700b [§83-3b]; Developmental Toxicity Study in Rabbits

Work Assignment No. 6-01-229 L (MRID 47372446)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Bldg 100, Ste B.
Durham, NC 27713

Primary Reviewer:
David A. McEwen, B.S.

Signature: David A. McEwen
Date: 11/30/09

Secondary Reviewer:
Michael E. Viana, Ph.D., D.A.B.T.

Signature: Michael E Viana
Date: 11/30/09

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.

Signature: Michael E Viana
Date: 11/30/09

Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T.

Signature: Steven Brecher
Date: 11/30/09

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This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang, PhD **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/22/11
EPA Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Lori Brunsman
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11
Template version 02/06

STUDY TYPE: Prenatal Developmental Toxicity Study in Rabbits (gavage); OPPTS 870.3700b ['83-3b]; OECD 414.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.6% a.i.; Lot/Batch # 08528/0002)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948;

CITATION: Kennel, P. (2006) AE C656948: Developmental toxicity study in the rabbit by Gavage. Bayer CropScience, Sophia Antipolis, France. Laboratory Project No. SA 05014, M-279773-01, ASB2008-5483; Nov. 06, 2006. MRID 47372446. Unpublished.

SPONSOR: Bayer CropScience

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 47372446), AE C656948 (Fluopyram, 94.6% a.i.; Lot/Batch # 08528/0002) in 0.5% aqueous methylcellulose 400 was administered via daily oral gavage in a dose volume of 4 mL/kg to 23 time-mated Zew Zealand White rabbits/dose group at doses of 0, 10, 25, or 75 mg/kg/day from gestation days (GD) 6-28. On GD 29, all surviving females were euthanized; each doe's uterus was removed via cesarean section and its contents examined. Fetuses were examined for external, visceral, and skeletal malformations and variations.

No compound-related effects were observed on mortality, clinical signs of toxicity, pregnancy rate, macroscopic findings, or liver parameters (weight or pathology).

On GD 21 one female at 75 mg/kg/day died and one control female was sacrificed due to accidental trauma on GD 15. Both deaths were attributable to a gavage error. The macroscopic observation showed hemorrhaging in the lung of both females together with hemorrhaging and foam in the trachea of one female and a trachea filled with fluid for the other female. In addition, one female was killed for humane reasons on GD 23 at 25 mg/kg/day, following a slight loss in body weight and a reduction in food consumption between GD 20 and 22. Clinical signs in this female consisted of a limited use of the right hindlimb on GD 22 and 23. The macroscopic observation showed a severe fracture of the right hindlimb, in association with massive subcutaneous hemorrhaging and a distal epiphysal femoral disjunction. The condition of this animal was considered to be due to accidental trauma.

At 75 mg/kg/day, mean body weight gain was decreased ($p<0.01$) between GD 14-18 (0.02 kg vs. 0.09 kg for controls) and between GD 18-22 (0.02 kg vs. 0.07 kg for controls). Thereafter, mean body weight gain was similar to the controls, resulting in an overall (GD 6-29) decreased (not significant)body weight gain of 35% (0.20 kg treated vs. 0.31 kg controls). Maternal corrected body weight change was decreased (not statistically significant) by 47% (-0.25 kg treated vs. -0.17 kg controls). Mean maternal food consumption was also reduced ($p<0.01$) by 22-34% at all intervals between GD 14-26.

The maternal LOAEL was 75 mg/kg/day based on decreased body weight gains (absolute and corrected) and food consumption. The maternal NOAEL is 25 mg/kg/day.

There were no treatment-related effects on abortions, premature deliveries, complete litter resorptions, or dead fetuses and no effects of treatment on the numbers of litters, live fetuses, early resorptions, or late resorptions. There were no treatment-related external, visceral, or skeletal variations or malformations.

At 75 mg/kg/day, mean fetal body weight was decreased ($p<0.05$) by 11% for both the combined and separate sexes.

The developmental LOAEL was 75 mg/kg/day based on decreased fetal body weights. The developmental NOAEL is 25 mg/kg/day.

This study is classified **acceptable/guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700b; OECD 414) in rabbits.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality Statements were included in the report.

DATA EVALUATION RECORD - SUPPLEMENT

FLUOPYRAM

Study Type: OPPTS 870.3800 ['83-4]; Reproductive Toxicity Study in Rats

Work Assignment No. 6-01-229 M (MRID 47372447)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
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Prepared by
Pesticides Health Effects Group
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Primary Reviewer:
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Signature: David A. McEwen
Date: 11/30/09

Secondary Reviewer:
Michael E. Viana, Ph.D., D.A.B.T.
Signature: Michael E Viana
Date: 11/30/09

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.
Signature: Michael E Viana
Date: 11/30/09

Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T.
Signature: Steven Brecher
Date: 11/30/09

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/23/11
EPA Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Lori Brunsman
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11
Template version 02/06

STUDY TYPE: Reproduction and Fertility Effects Study in Rats
OPPTS 870.3800 ['83-4]; OECD 416.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.7% a.i.; Lot/Batch # 08528/0002)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948;

CITATION: Milius, A.; Bommegowda, S. (2008) Technical Grade AE C656948: A two generation reproductive toxicity study in the Wistar rat. Bayer CropScience LP, Stilwell, KS. Study No. 06-R72-DX; Report No.: 201855, M-299334-01, ASB2008-5478. March 27, 2008. MRID 47372447. Unpublished.

Milius, A (2008) Technical Grade AE C656948: A dose-range finding reproductive toxicity study in the Wistar rat. Bayer CropScience LP, Stilwell, KS. Study ID: 05-P72-BQ. March 26, 2008. MRID 47372448. Unpublished.

SPONSOR: Bayer CropScience

EXECUTIVE SUMMARY: In a two-generation reproduction toxicity study (MRID 47372447), AE C656948 (Fluopyram, 94.7% a.i.; Lot/Batch # 08528/0002) was administered continuously in the diet at dose levels of 0, 40, 220, or 1200 ppm (equivalent to 0/0, 2.65/3.15, 14.5/17.2, and 82.8/96.0 mg/kg/day in males/females, respectively) for two consecutive generations. The P generation animals (30/sex/dose group) were fed the test diets for 10 weeks prior to mating to produce the F1 litters. F1 offspring selected to be parents of the next generation (30/sex/dose group) were fed the same test diet concentrations as their parents. F1 parents were fed the test diets for 10 weeks prior to mating to produce the F2 generation. The F2 offspring were terminated after weaning.

There were no effects of treatment on mortality, clinical signs of toxicity, or food consumption in either sex in either generation during pre-mating. Furthermore, no treatment-related effects on body weight gain or food consumption were observed during gestation or lactation in either generation. No treatment-related gross necropsy findings were observed in either sex in either generation.

During pre-mating (Weeks 1-10), body weight gains were decreased by 20 and 10% in the 1200 ppm females of the P and F1 generations, respectively. Additionally in the P generation females, decreases in body weight were observed at 1200 ppm during Days 0-13 of gestation (decr 5-6%) and on Day 0 of lactation (decr 5%).

At 1200 ppm, treatment-related clinical chemistry findings were limited to increased creatinine, total protein, and albumin in the P-generation males, increased urea nitrogen and total protein in F1 males, and increased cholesterol in the F1 females. Additionally at this dose, hematology changes included decreased hemoglobin and hematocrit in the P-generation females, decreased hemoglobin in F1 females, and increased white blood cell and monocyte counts in the F1 females.

In both the P- and F1 generations, test substance-related increases were noted at 1200 ppm in absolute and relative kidney (right and left) weights in the males, and absolute and relative liver weights in both sexes. Additionally in the F1 females, absolute and relative spleen weights were decreased at 1200 ppm and relative spleen weight was also decreased in 220 ppm. It was stated that the decreases in spleen weights (absolute and/or relative) in the F1 females were not associated with corresponding micropathology findings. However, as white blood cell parameters were changed in F1 animals and spleen weights were later found to be affected in F1 and F2 pups as well, this finding may be treatment related and further studies may be required to clarify reasons for this observation.

In the P-generation, test substance-related micropathology findings noted at 1200 ppm included increased incidence of protein droplet nephropathy and lymphocytic infiltration in the kidneys of the males, and increased incidence of centrilobular hypertrophy in the livers of both sexes. It was stated that these findings were in accordance with findings of other studies over a similar duration.

The LOAEL for parental toxicity is 1200 ppm (equivalent to 82.8/96.0 mg/kg/day in males/females, respectively) based on: decreases in body weight gain during pre-mating in the P- and F1 generation females; decreased body weights during gestation and lactation in P generation females; clinical chemistry effects (increased creatinine, total protein, albumin and urea nitrogen in males and increased cholesterol in F1 females); hematology effects (decreased hemoglobin and hematocrit in the P-generation females, decreased hemoglobin in F1 females, and increased white blood cell and monocyte counts in the F1 females); increased kidney weight associated with an increased incidence of protein droplet nephropathy and lymphocytic infiltration in P- and F1 generation males; and increased liver weights associated with an increased incidence of centrilobular hypertrophy in both sexes. The NOAEL is 220 ppm (equivalent to 14.5/17.2 mg/kg/day in males/females, respectively).

There were no treatment-related effects on: viability, clinical signs, birth or live birth indices; lactation index, or pup sex ratio for either generation. Vaginal patency was similar to controls in the F1 females, and anogenital distance on PND 0 was unaffected by treatment in the F2 pups. There were no treatment-related macroscopic or microscopic findings in the F1 or F2 pups.

At 1200 ppm, F1 pup body weights (combined male and female) were decreased (not significant [NS]) by 5% on PND 14 and 21, resulting in a 5% decreased in overall (PND 0-21) body weight gain. F2 pup body weights were decreased (NS, except p<=0.05 on PND 21) by 6-8% on PND 4-21. Overall body weight gain throughout lactation was also decreased by 9% in these animals.

At 1200 ppm, test substance-related decreases in organ weights in F2 generation pups were limited to decreased absolute and relative spleen and thymus weights in males, females, and combined pups.

A slight delay in preputial separation in the 1200 ppm F1 males was observed (42.5 days) compared to controls. It was stated that although statistically significant, the number of days to criteria was within the range of historical controls (40.7-44.0 days). Therefore, this finding was considered secondary to the reduced body weight observed in the males during lactation.

The LOAEL for offspring toxicity is 1200 ppm (equivalent to 82.8/96.0 mg/kg/day in males/females, respectively) based on decreased pup body weights and overall body weight gains in the F1 and F2 generations, and decreased spleen and thymus weights in both sexes in the F2 generation. The NOAEL is 220 ppm (equivalent to 14.5/17.2 mg/kg/day in males/females, respectively).

There were no effects of treatment in either generation on: estrous cycle number or length, sperm parameters (motility, counts, or morphology), mating, fertility or gestation indices, days to insemination, gestation length, or the median number of implants. Ovarian follicle counts in the F1 females were similar to controls.

The LOAEL for reproductive toxicity was not observed. The NOAEL is 1200 ppm (equivalent to 82.8/96.0 mg/kg/day in males/females, respectively).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality Statements were included in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: OPPTS 870.4100; '83-1b, Chronic Oral Toxicity Study in Dogs

Work Assignment No. 6-1-229 H (MRID 47372449)

Prepared for
Health Effects Division
Office of Pesticide Programs
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2777 South Crystal Drive
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Prepared by
Pesticides Health Effects Group
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1910 Sedwick Road, Building 100, Suite B
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Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Date:	Michael E Viana *11/10/09*
Secondary Reviewer: John W. Allran, M.S.	Signature: Date:	John W Allran *11/10/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Date:	Michael E Viana *11/10/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Date:	Steven Brecher *11/10/09*

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EPA Reviewer: Whang Phang **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11

Template version 02/06

DATA EVALUATION RECORD

STUDY TYPES: Chronic Oral (Diet) Toxicity Study in Dogs; OPPTS 870.4100b ['83-1b]; OECD 452.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.6%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Kennel, P. (2007) AE C656948: chronic toxicity study in the dog by dietary administration. Bayer CropScience, Sophia Antipolis Cedex, France. Laboratory Report Nos.: SA 05047, M-294279-01, ASB2008-5363; Nov. 02, 2007. MRID 47372449. Unpublished

SPONSOR: Bayer CropScience, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a chronic oral toxicity study (MRID 47372449), fluopyram (94.6% a.i., Batch 08528/0002) was administered in the diet to four beagle dogs/sex/dose group at dose levels of 0, 100, 400, or 2000 ppm (equivalent to 0/0, 3.0/3.8, 13.2/14.4, and 67.6/66.1 mg/kg/day in males/females) for at least 1 year.

There were no effects of treatment observed on mortality, clinical signs, ophthalmoscopic examinations, hematology, urinalysis, or gross pathology.

At 2000 ppm, body weight losses were observed in both sexes during Week 1 (-0.2 kg and -0.1 kg in males and females, respectively, compared to gains of +0.1 kg, and 0.0 kg in control males and females). These body weight losses corresponded to decreased food consumption (decr. 30% and 24% in males and females, respectively) during Week 1. The decrease in food consumption persisted in females until the end of the study. Additionally at 2000 ppm, alkaline phosphatase was increased by 58-187% in males and females at Weeks 3, 6, and 12, and minimal diffuse centrilobular hepatocellular hypertrophy was observed microscopically in 3/4 males.

The LOAEL was 2000 ppm (equivalent to 67.1/66.1 mg/kg/day in males/females) based decrease in food consumption and corresponding slight decrease in body weight, increases in alkaline phosphatase and centrilobular hepatocellular hypertrophy. NOAEL was 400

ppm (13.2/14.4 mg/kg/day in males/females).

This study is considered **acceptable/guideline** and satisfies the requirements (OPPTS 870.4100b; OECD 452) for a subchronic toxicity study in dogs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality Statements were included in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: OPPTS 870.4200b, '83-2b; Carcinogenicity Study in Mice

Work Assignment No. 6-1-229 J (MRID 47372450)

Prepared for
Health Effects Division
Office of Pesticide Programs
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Prepared by
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Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/25/09*
Secondary Reviewer: David A. McEwen, B.S.	Signature: David A McEwen Date: *11/25/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/25/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Steven Brecher Date: *11/25/09*

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This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/'11
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPES: Carcinogenicity Oral (Diet) Toxicity Study in Mice; OPPTS 870.4200b ['83-2b]; OECD 451.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (≥94.5%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Wason, S.M. (2007) AE C656948: carcinogenicity study of AE C656948 in the C57BL/6J mouse by dietary administration. Performing Laboratory: Bayer CropScience, Sophia Antipolis, France. Laboratory Report Nos.: SA 05094, M-295688-01, ASB2008-5440. Dec. 14, 2007. MRID 47372450. Unpublished

SPONSOR: Bayer CropScience, Alfred Nobel Str. 50, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In a carcinogenicity study (MRID 47372450), AE C656948 (≥94.5% a.i., Batch 08528/0002) was administered in the diet to 50 C57BL/6J mice/sex/dose group at dose levels of 0, 30, 150, or 750 ppm (equivalent to 0/0, 4.2/5.3, 20.9/26.8, and 105/129 mg/kg day in males/females) for up to 78 weeks. In addition, an interim sacrifice was performed at Week 52 on groups of 10 mice/sex/dose that were treated as above.

There were no unscheduled deaths or clinical signs occurring during the study that could be attributed to treatment. The survival rate was not different among the control and dose groups. Body weight gain was decreased only in the 150 ppm and above males and only during the second trimester of the study (weeks 26 to 54). Afterwards, some compensatory growth was observed resulting in a mean final body weight that was similar to the control group value.

Mean absolute and relative **liver** weights were markedly increased in the 150 ppm and above males and females at interim sacrifice as well as at study termination. The increment exhibited a clear dose response. At these dose levels, gross necropsy findings such as dark and enlarged livers were corroborated by an increase in non-neoplastic histopathological lesions such as centrilobular to panlobular hypertrophy, hepatocellular cholestasis, single cell degeneration/necrosis or eosinophilic foci. A few of these non-neoplastic effects on the liver

were observed only in males pointing to a higher vulnerability of this sex with regard to hepatotoxicity.

Toxic effects on the **thyroid** were noted at 750 ppm in both males and females and in the 150 ppm males. The main non-neoplastic finding, follicular cell hyperplasia, was apparent in male mice at the interim sacrifice.

Mean absolute and relative **kidney** weights were decreased at the 750 ppm dose level in both sexes. In addition, a higher incidence and/or severity of bilateral cortical basophilic tubules, hyaline casts(s) and interstitial mononuclear cell infiltrates, glomerular congestion/ hemorrhage(s), and more pronounced amyloid deposition (mainly in the glomerular interstitium) was noted at this dose but only in females.

At 30 ppm, mean absolute and relative liver weight was higher in the males than in the control group, but by less than 10 % although the difference was statistically significant. More important, this organ weight increase was not accompanied by liver cell hypertrophy. The only histopathological finding in the liver at this dose level was diffuse centrilobular vacuolation. Therefore, these minor findings were not considered adverse.

The LOAEL is 150 ppm (equivalent to 20.9/26.8 mg/kg/day in males/females), based on liver and thyroid toxicity as described above. The NOAEL is 30 ppm (equivalent to 4.2/5.3 mg/kg/day in males/females).

At the doses tested, there was a treatment-related increase in tumor incidence compared to controls. A higher incidence ($p<=0.05$) of follicular cell adenoma was observed in the 750 ppm males (7/50) as compared to the controls (1/50). Dosing was considered adequate based on the findings of liver and thyroid toxicity as described above.

This study is considered **acceptable/guideline** and satisfies the requirements (OPPTS 870.4200b; OECD 451)for a combined chronic toxicity / carcinogenicity study in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality Statements were included in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: OPPTS 870.4300, '83-5;
Combined Chronic Toxicity / Carcinogenicity Study in Rats

Work Assignment No. 6-1-229 I (MRID 47372501)

Prepared for
Health Effects Division
Office of Pesticide Programs
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Prepared by
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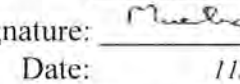
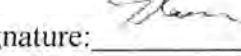
Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Date:	 *11/25/09*
Secondary Reviewer: David A. McEwen, B.S.	Signature: Date:	 *11/25/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Date:	 *11/25/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Date:	 *11/25/09*

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.EPA Reviewer: Whang Phang **Signature:** W Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Lori Brunsman
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPES: Combined Chronic Toxicity / Carcinogenicity Oral (Diet) Toxicity Study in Rats; OPPTS 870.4300 ['83-5]; OECD 453.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.5%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Kennel, P. (2008) AE C656948: chronic toxicity and carcinogenicity study of AE C656948 in the Wistar rat by dietary administration. Performing Laboratory: Bayer CropScience, Sophia Antipolis Cedex, France. Laboratory Report Nos.: SA 04312, M-298339-01, ASB2008-5439; Feb. 29, 2008. MRID 47372501. Unpublished

SPONSOR: Bayer CropScience, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a combined chronic toxicity / carcinogenicity study (MRID 47372501), AE C656948 (94.5% a.i., Batch 08528/0002) was administered in the diet to 60 Wistar (Rj: WI [IOPS HAN]) rats/sex/dose group at dose levels of 0, 30, 150, 750 (males only), or 1500 (females only) ppm (equivalent to 0/0, 1.20/1.68, 6.0/8.6, 29 (males), and 89 (females) mg/kg day in males/females) for up to 24 months. In the 750 ppm males, the dose level was reduced to 375 ppm from Week 85 onward due to increased mortality. In addition, an interim sacrifice was performed at Week 52 on groups of 10 rats/sex/dose that were treated as above.

At 1500 ppm (females only), increased incidence of hair loss and wasted appearance was noted. Mean body weights were significantly reduced in both sexes.

At 750/375 ppm (males only), there was a statistically significant increase in mortality at Week 52 and after 24 months, although no clear cause for these premature deaths could be established. Mean body weight was significantly reduced in both sexes at various time during the study..

Liver toxicity became apparent by an increase in organ weight at 150 ppm and above in male rats and at 1500 ppm in females that was sometimes accompanied. Clinical chemistry findings suggesting hepatotoxicity were minor in nature and were observed at 750/375 and 1500 ppm.

They comprised occasionally higher mean triglyceride concentrations and slightly lower mean glucose concentrations in the females. Activity of alkaline phosphatase was reduced in both sexes throughout the study but achieved statistical significance only occasionally. Histological changes included a higher incidence of altered hepatocytes (eosinophilic foci) and hepatocellular brown pigments, focal or multifocal hepatocellular vacuolation, increased number of mitoses, centrilobular to panlobular hypertrophy and hepatocellular single cell necrosis, with females being much more affected. At 150 ppm, however, histopathological finding (hypertrophy) was confined to male rats corresponding to the increased organ weight noted at this dose.

In the **kidney**, marked degenerative changes such as chronic progressive nephropathy or focal/multifocal (medullar or cortical) tubular dilatation, together with an increased incidence of tubular golden/brown pigments (mainly in females) and collecting ducts hyperplasia, were observed at the high dose. In addition, a higher incidence of hyaline droplets and of renal cysts was noted in male rats. At the mid dose level of 150 ppm, male rats still displayed a higher frequency of tubular hypertrophy or dilatation. During the first year of treatment, but not thereafter, urinalysis revealed higher incidences of abnormal color of urine (orange to red) in females and a higher incidence and severity of cellular casts in males. This latter finding was also confirmed in male rats receiving the intermediate dose.

Effects of AE C656948 on the **thyroid gland** were demonstrated by increased organ weights at the highest dose level in both sexes that were associated with histopathological changes (follicular cell hyperplasia and/or hypertrophy and colloid alteration/depletion). At 150 ppm, colloid alteration was noted in the females, and follicular cell hypertrophy was observed in the males. Both findings were reduced in frequency and severity compared to the high dose groups.

The **eyes** were affected by long-term treatment was seen in treated animals at 150 ppm or above. Ophthalmologic examination revealed abnormal color of the retinal fundus in females after 12 months. At the 24-month examination, this condition was observed in females and males, together with small retinal vessels. In addition, hyperreflectivity in the retina was noted in females and corneal opacity, edema of the cornea and nuclear opacity in males. These effects were more severe at the top dose level and less pronounced but still present after 2 years in the male and female groups receiving 150 ppm. Histologically, bilateral retinal atrophy was noted at the highest dose level, together with a higher incidence of lens degeneration.

A tendency towards lower erythrocyte parameters (hemoglobin concentration, mean corpuscular volume, hematocrit and/or mean corpuscular hemoglobin) was observed in the 1500 ppm females throughout the study confirming evidence from short-term studies that the red blood cells might be an additional target. The same tendency was observed in 750/375 ppm males at most time points; however, statistical significance was not achieved. The assumption of an effect on the blood was further substantiated by a more frequent occurrence of extramedullary hematopoiesis in the livers of high dose females.

The LOAEL is 150 ppm (6.0mg/kg/day) based on nephropathy, follicular cell hypertrophy in the thyroid, eye effect, and liver effect characterized by increased liver weight, gross and hispathological findings. The NOAEL is 30 ppm (1.2 mg/kg/day).

At the doses tested, there was a treatment-related increase in tumor incidence compared to controls. At the end of the 2-year carcinogenicity phase, the incidence of liver cell tumors (carcinoma and adenoma) was significantly increased in females receiving 1500 ppm. The combined incidence of female rats with benign and malign liver tumors was 11 (including 3 animals with carcinoma) as compared to 2 in each of the control, low and mid dose groups. No such increment was seen in male rats but the very different actual compound intakes do not allow for a meaningful comparison. Dosing was considered adequate based on the findings of liver, kidney, thyroid, and ocular toxicity as described above.

This study is considered **acceptable/guideline** and satisfies the requirements (OPPTS 870.4300; OECD 453) for a combined chronic toxicity / carcinogenicity study in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality Statements were included in the report.

DATA EVALUATION RECORD - SUPPLEMENT

FLUOPYRAM

Study Type: OPPTS 870.5100 [§84-2]; Bacterial Reverse Gene Mutation Assay

Work Assignment No. 6-01-229 P (MRID 47372502)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Bldg 100, Ste B.
Durham, NC 27713

Primary Reviewer:
David A. McEwen, B.S.

Signature: David A. McEwen
Date: 11/10/09

Secondary Reviewer:
Michael E. Viana, Ph.D., D.A.B.T.

Signature: Michael E Viana
Date: 11/10/09

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.

Signature: Michael E Viana
Date: 11/10/09

Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T.

Signature: Steven Brecher
Date: 11/10/09

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
EPA Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Myron Ottley
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11

STUDY TYPE: *In vitro* Bacterial Gene Mutation (*Salmonella typhimurium*)/ mammalian activation gene mutation assay; OPPTS 870.5100 ['84-2]; OECD 471 (formerly OECD 471 & 472).

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.7% a.i.; Lot/Batch # 08528/0002)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948;

CITATION: Wirnitzer, U. (2006) AE C656948: *Salmonella*/microsome test, plate incorporation and pre-incubation method. Bayer HealthCare AG, PH- R&D Toxicology, Germany. Report No.: AT02911, M-269978-01, ASB2008-5552. Jan. 12, 2006. MRID 47372502. Unpublished.

SPONSOR: Bayer CropScience AG, Alfred Nobel Str. 50, 40789 Monheim, Germany.

EXECUTIVE SUMMARY: In two independent trials of a reverse gene mutation assay in bacteria (MRID 47372502), *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 were exposed to AE C656948 (Fluopyram, 94.7% a.i.; Lot/Batch # 08528/0002) in dimethylsulfoxide (DMSO) at concentrations of 0, 16, 50, 158, 500, 1581, or 5000 µg/plate both in the presence and absence of S9-activation. The S9 fraction was derived from the livers of male Sprague-Dawley rats induced with Aroclor 1254. The standard plate incorporation method was used in the initial trial and the pre-incubation method was used in the confirmatory assay. Standard strain-specific mutagens served as positive controls.

AE C656948 was tested up to the limit dose (5000 µg/plate). Precipitation of the test material was observed at 1581 µg/plate and above; however, assessment was still possible up to the highest dose of 5000 µg/plate (+/-S9). There was no evidence of cytotoxicity at any concentration with or without S9. There were no marked increases in the mean number of revertants/plate in any strain in either trial in the presence or absence of S9. The positive controls induced the appropriate response in all strains (+/-S9). **There was no evidence of induced mutant colonies over background.**

The study is classified as **acceptable/guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5100 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.

DATA EVALUATION RECORD - SUPPLEMENT

FLUOPYRAM

Study Type: OPPTS 870.5100 [§84-2]; Bacterial Reverse Gene Mutation Assay

Work Assignment No. 6-01-229 Q (MRID 47372503)

Prepared for
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U.S. Environmental Protection Agency
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Prepared by
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Primary Reviewer: David A. McEwen, B.S.	Signature: David A. McEwen Date: 11/30/09
Secondary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: 11/30/09
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: 11/30/09
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Date: 11/30/09

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EPA Reviewer: Whang Phang **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/27/11
EPA Work Assignment Manager: Myron Ottley, Ph.D. **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/'11

STUDY TYPE: *In vitro* Bacterial Gene Mutation (*Salmonella typhimurium/ E. coli*)/ mammalian activation gene mutation assay; OPPTS 870.5100 ['84-2]; OECD 471 (formerly OECD 471 & 472).

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (95.7% a.i.; Lot/Batch # 2007-010986)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948;

CITATION: Herbold, B. (2008) AE C656948: Salmonella/microsome test, plate incorporation and pre-incubation method. Bayer HealthCare AG, BSP-GDD-GED-GTOX Genetic Toxicology, Germany. Report No.: AT04419, M-298529-01, ASB2008-5554. Feb. 15, 2008. MRID 47372503. Unpublished.

SPONSOR: Bayer CropScience AG, Alfred Nobel Str. 50, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In two independent trials of a reverse gene mutation assay in bacteria (MRID 47372503), *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 were exposed to AE C656948 (Fluopyram, 95.7% a.i.; Lot/Batch # 2007-010986) in dimethylsulfoxide (DMSO) at concentrations of 0, 16, 50, 158, 500, 1581, or 5000 µg/plate (initial trial) and 0, 5, 16, 50, 158, 500, or 1581 µg/plate (confirmatory assay) both in the presence and absence of S9-activation. The S9 fraction was derived from the livers of male Sprague-Dawley rats induced with Aroclor 1254. The standard plate incorporation method was used in the initial trial and the pre-incubation method was used in the confirmatory assay. Standard strain-specific mutagens served as positive controls.

AE C656948 was tested up to cytotoxic concentrations. It was stated that the test material induced strain-specific toxicity at 500 µg/plate and above; however, concentrations up to 1581 µg/plate could be used for reliable assessment. There were no marked increases in the mean number of revertants/plate in any strain in either trial in the presence or absence of S9. The positive controls induced the appropriate response in all strains in the presence and absence of S9-activation. **There was no evidence of induced mutant colonies over background.**

The study is classified as **acceptable/guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5100 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.

DATA EVALUATION RECORD - SUPPLEMENT

FLUOPYRAM

Study Type: OPPTS 870.5300 [§84-2]; V79 Cells /Mammalian Activation Gene Forward Mutation Assay at the HGPRT Locus

Work Assignment No. 6-01-229 R (MRID 47372504)

Prepared for
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Date: 11/30/09

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Signature: Michael E Viana
Date: 11/30/09

Program Manager:
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Signature: Michael E Viana
Date: 11/30/09

Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T.
Signature: Steven Brecher
Date: 11/30/09

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EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
EPA Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Lori Brunsman
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/'11

STUDY TYPE: *In vitro* Mammalian Cell Gene Mutation Assay in Chinese Hamster V79 Cells; OPPTS 870.5300 [§84-2]; OECD 476.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.7% a.i.; Lot/Batch # 08528/0002)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948;

CITATION: Herbold, B. (2006) AE C656948: V79/HPRT-test *in vitro* for the detection of induced forward mutations. Bayer Healthcare AG, PH-GDD Toxicology, Germany. Report No.: AT02875, M-268775-01, ASB2008-5556. Feb. 8, 2006. MRID 47372504. Unpublished.

SPONSOR: Bayer CropScience AG, Alfred Nobel Str. 50, 40789 Monheim, Germany.,

EXECUTIVE SUMMARY: In a mammalian cell gene mutation assay at the HGPRT locus (MRID 47372504), V79 lung fibroblast cells cultured *in vitro* were exposed to AE C656948 (Fluopyram, 94.7% a.i.; Lot/Batch # 08528/0002) in dimethylsulfoxide (DMSO) at concentrations of 0, 4, 8, 16, 32, 64, 128, or 256 µg/mL (+/-S9) for 5 hours. The S9 fraction was derived from the livers of male Sprague-Dawley rats induced with Aroclor 1254. The positive controls were ethyl methanesulfonate (-S9) and dimethylbenzanthracene (+S9).

AE C656948 was tested up to the limit of solubility. Precipitation of the test material was observed at 128 µg/mL and above both in the presence and absence of S9. No marked increase in mutant frequency was observed in the presence or absence of S9-activation. The positive controls induced the appropriate response (+/-S9). **There was no evidence of induced mutant colonies over background in the presence or absence of S9-activation.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.5300; OECD 476) for *in vitro* mutagenicity (mammalian forward gene mutation) data.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.

DATA EVALUATION RECORD - SUPPLEMENT

FLUOPYRAM

Study Type: OPPTS 870.5375 [§84-2]; *In Vitro* Chromosomal Aberration Assay in Chinese Hamster V79 Cells

Work Assignment No. 6-01-229 S (MRID 47372505)

Prepared for
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U.S. Environmental Protection Agency
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Prepared by
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Program Manager:
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Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T.
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Date: 11/30/09

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EPA Reviewer: Whang Phang **Signature:** [signature]
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
EPA Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** [signature]
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11

STUDY TYPE: *In vitro* Mammalian Cytogenetics (Chromosomal Aberration Assay in Rat Lymphocytes) OPPTS 870.5375 [§84-2]; OECD 473.

PC CODE: 080302 **DP BARCODE:** D353273

TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.7% a.i.; Lot/Batch # 08528/0002)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948;

CITATION: Nern, M. (2005) AE C656948: *In vitro* chromosome aberration test with Chinese hamster V79 cells. Bayer Healthcare AG, PH- R&D Toxicology, Germany. Report No.: AT02798, M-266066-01, ASB2008-5555. Dec. 15, 2005. MRID 47372505. Unpublished.

SPONSOR: Bayer CropScience AG, Alfred Nobel Str. 50, 40789 Monheim, Germany.

EXECUTIVE SUMMARY: In a mammalian cell cytogenetics assay (chromosome aberration; MRID 47372505), Chinese hamster V79 cell cultures were exposed to AE C656948 (Fluopyram, 94.7% a.i.; Lot/Batch # 08528/0002) in dimethylsulfoxide (DMSO) at concentrations of 0, 30, 60, 120, 180, or 240 µg/mL for 4 hours (with a 14- or 26-hour recovery period) in the presence of S9 and 18 hours of continuous exposure in the absence of S9. Cells were harvested at 18 or 30 hours after initiation of dosing (+S9) and 18 hours after initiation of dosing (-S9). The positive controls were mitomycin C (-S9) and cyclophosphamide (+S9).

AE C656948 was tested up to the limit of solubility. Precipitation of the test material was observed at 120 µg/mL and above both in the presence and absence of S9. Based on the observed cytotoxicity (as indicated by decreased survival), cultures at concentrations of 60, 120, and 180 µg/mL (+/-S9) were selected for evaluation of chromosomal aberrations. No biologically relevant or statistically significant increases in the number of metaphases with aberrations were observed at any concentration at any harvest time in the presence or absence of S9. The positive controls induced the appropriate response in the presence and absence of S9. **There was no evidence of chromosome aberrations induced over background in the presence or absence of S9-activation.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.5375; OECD 473) for *in vitro* mutagenicity (chromosome aberration) data.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were presented in the report.

DATA EVALUATION RECORD - SUPPLEMENT

FLUOPYRAM

Study Type: OPPTS 870.5395 [§84-2]; Micronucleus Assay in Mice

Work Assignment No. 6-01-229 T (MRID 47372506)

Prepared for
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Office of Pesticide Programs
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Date: 11/30/09

Program Manager:
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Date: 11/30/09

Quality Assurance:
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Date: 11/30/09

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EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
EPA Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Myron Ottley
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11

STUDY TYPE: *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus Assay in Mice; OPPTS 870.5395 ['84-2]; OECD 474.

PC CODE: 080302 **DP BARCODE:** D353273

TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.7% a.i.; Lot/Batch # 08528/0002)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948;

CITATION: Herbold, B. (2005) AE C656948: Micronucleus test on the male mouse. Bayer HealthCare AG, PH- R&D Toxicology, Germany. Report No.: AT02753, M-263710-01, ASB2008-5557. Dec. 2, 2005. MRID 47372506. Unpublished.

SPONSOR: Bayer CropScience

EXECUTIVE SUMMARY: In a bone marrow micronucleus assay (MRID 47372506), young adult male NMRI mice (5/dose) were treated twice (24 hours apart) via i.p. injection (volume not reported) with AE C656948 (Fluopyram, 94.7% a.i.; Lot/Batch # 08528/0002) in 0.5% aqueous Cremophor at doses of 0, 250, 500, or 1000 mg/kg. Bone marrow cells were harvested at 24 hours after final dosing. Cyclophosphamide (single i.p. injection) served as the positive control.

All animals survived to scheduled sacrifice. Clinical signs including apathy, semi-anesthetized state, roughened fur, weight loss, sternal recumbency, spasm, body stretching, and difficulty in breathing were observed at all dose levels until sacrifice. There was an increase in the number of normochromatic erythrocytes in all fluopyram treated groups compare to controls although the difference was only statistically significant at 1000 mg/kg. This demonstrated a relevant and sufficient systemic exposure of the animals to the test substance. The MPCE frequency was comparable between vehicle controls and all treated groups. The positive control induced the appropriate response. **There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.5395; OECD 474) for *in vivo* cytogenetic mutagenicity data.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were presented in the report.

DATA EVALUATION RECORD - SUPPLEMENT

FLUOPYRAM

Study Type: OPPTS 6200a [§81-8], Neurotoxicity Screening Battery in Rats

Work Assignment No. 6-01-229 N (MRID 47372507)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Date: 11/30/09

Secondary Reviewer:
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Signature: Michael E Viana
Date: 11/30/09

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.

Signature: Michael E Viana
Date: 11/30/09

Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T.

Signature: Steven Brecher
Date: 11/30/09

Disclaimer

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EPA Reviewer: Whang Phang **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/23/11
EPA Work Assignment Manager: Myron Ottley, Ph.D. **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11
Template version 02/06

STUDY TYPE: Acute Neurotoxicity - Rats OPPTS 870.6200a [' 81-8]; OECD 424.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.7% a.i.; Lot/Batch # 08528/0002)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948;

CITATION: Gilmore, R. G. and Hoss, H. E. (2007): An acute Oral Neurotoxicity Screening Study with Technical Grade AE C656948 in Wistar Rats. Bayer CropScience LP, Stilwell, KS. Study No. 06-N12-EK. Report No.: 201656, M-289073-01, ASB2008-5365. June 8, 2007. MRID 47372507. Unpublished.

SPONSOR: Bayer CropScience

EXECUTIVE SUMMARY: In an acute neurotoxicity study (MRID 47372507), groups of 12 non-fasted young adult Wistar rats/sex/dose were given a single oral gavage dose (10 mL/kg) of Fluopyram (94.7% a.i.; Lot/Batch # 08528/0002) in aqueous 2% (v/v) Cremophor EL at dose levels of 0, 125, 500, or 2000 mg/kg (limit dose) and were observed for 14 days. Neuro-behavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in all rats at one week prior to dosing and on Days 0 (approximately 1 hour post-dosing), 7, and 14. At study termination, all animals were necropsied, and 6 rats/sex/dose were euthanized and perfused *in situ* for neuropathological examination. The brain and peripheral nervous system tissues collected from the perfused animals in the control and 2000 mg/kg groups were subjected to histopathological evaluation. Because motor and locomotor activity were impaired in females even at the lowest dose level of 125 mg/kg, a follow-up study was initiated in order to establish a clear NOAEL. For this purpose, 12 females/group were treated in the same manner as in the initial study at dose levels of 0, 25, 50, or 100 mg/kg. In-life observations were limited to FOB and motor activity measurements at one week prior to dosing and on Day 0 (approximately 1 hour post-dosing). The animals were sacrificed at 2 or 3 days post-dosing and were discarded without further examinations. Positive control data were not provided.

There were no compound-related effects on mortality, body weight, brain weight (absolute and relative), and gross or neuropathology observed at any dose.

In the initial study, compound-related clinical signs were limited to urine stain in 4/12 males at 2000 mg/kg. In the FOB on Day 0, mean body temperature was decreased in the 500 and 2000 mg/kg females (37.4°C and 36.9°C, respectively vs. 37.9°C for controls). At 500 and 2000 mg/kg, total session motor and locomotor activity were decreased by 51-72% and 49-77%, respectively, in both sexes on Day 0. Additionally in the 125 mg/kg females, total session motor and locomotor activity were decreased by 26-31% on Day 0.

In the follow-up study, total session motor and locomotor activity were decreased by 38% each in the 100 mg/kg females on Day 0.

The LOAEL is 100 mg/kg, based on decreased motor and locomotor activity in the females. The NOAEL is 50 mg/kg.

The initial study is considered to be acceptable whereas the follow-up study in females is only supplementary. However, because a full study in both sexes is available, the information obtained from both experiments, when taken together, is considered complete and sufficient to address this annex point. This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.6200a; OECD 424) for an acute neurotoxicity study in the rat.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.

DATA EVALUATION RECORD - SUPPLEMENT

FLUOPYRAM

Study Type: OPPTS 6200b [§82-7], Subchronic Neurotoxicity Study in Rats

Work Assignment No. 6-01-229 O (MRID 47372508)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Bldg 100, Ste B.
Durham, NC 27713

Primary Reviewer: David A. McEwen, B.S.	Signature: David A. McEwen Date: 11/30/09
Secondary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: 11/30/09
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: 11/30/09
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Steven Brecher Date: 11/30/09

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
EPA Work Assignment Manager: Myron Ottley, Ph.D. **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11
Template version 02/06

STUDY TYPE: Subchronic Neurotoxicity - Rats OPPTS 870.6200b [' 82-7]; OECD 424.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.7% a.i.; Lot/Batch # 08528/0002)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948;

CITATION: Gilmore, R. G. (2008): A Subchronic Neurotoxicity Screening Study with Technical Grade AE C656948 in Wistar Rats. Bayer CropScience LP, Stilwell, KS. Repot No.: 201833; Study No.: 07-N72-IV. M-299110-01, ASB2008-5366, March 11, 2008. MRID 47372508. Unpublished.

SPONSOR: Bayer CropScience

EXECUTIVE SUMMARY: In a subchronic neurotoxicity study (MRID 47372508), groups of 12 young adult Wistar rats/sex/dose were exposed to Fluopyram (94.7% a.i.; Lot/Batch # 08528/0002) in the diet at nominal concentrations of 0, 100, 500, or 2500 ppm (equivalent to 0/0, 6.69/8.05, 33.2/41.2, and 164.2/197.1 mg/kg/day, M/F) for 13 weeks. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in all rats at one week prior to dosing and during Weeks 2, 4, 8, and 13. At study termination, all rats were necropsied, and 6 rats/sex/dose were euthanized and perfused *in situ* for neuropathological examination. The brain and peripheral nervous system tissues collected from the perfused animals in the control and 2500 ppm groups were subjected to histopathological evaluation. Positive control data were not provided; however, it was stated that previous studies conducted at this laboratory had demonstrated the sensitivity of the test system and the methods used, as well as the adequacy of training of technical personnel.

There were no compound-related effects on mortality, clinical signs of toxicity, ophthalmoscopic examinations, FOB parameters, motor or locomotor activity, brain weight (absolute and relative), and gross or neuropathology observed at any dose.

At 2500 ppm, body weights were decreased by 4-7% in males and 5-12% in females from Day 21 throughout the remainder of the study. Overall (Days 0-91) body weight gains were decreased by 10% in males and 26% in females. Additionally at this dose, food consumption was decreased by 15% in the males on Day 21 and by 13-24% in the females from Day 21 throughout the

remainder of the study. Compound-related increases in clinical chemistry parameters included: (i) cholesterol (incr 44-69%) in both sexes; (ii) triglycerides (incr 90%) in females; (iii) protein (incr 9%) in females; (iv) globulin (incr 16%) in females; and (v) albumin (incr 10%) in males. Additionally, glucose levels were decreased by 6-15% in both sexes at this dose. The findings in clinical chemistry were likely due to changes in liver function induced by Fluopyram, as well known from other studies with this compound at comparable dose levels. In the 2500 ppm females, compound-related decreases in hematology parameters included: (i) hemoglobin (decr 10%); (ii) mean corpuscular hemoglobin (MCH, decr 14%); (iii) mean corpuscular volume (MCV, decr 13%); and (iv) hematocrit (decr 9%). Additionally, hemoglobin distribution width (HDW) was increased by 28% in females at this dose.

At 500 ppm, decreased food consumption (decr 7-12%) was observed in females on Days 21-42, 63-70, and 91. However, these decreases did not result in significant decreases in body weights or body weight gain in this group.

No evidence of neurotoxicity was observed in either sex at any dose.

The LOAEL is 2500 ppm (164.2/197.1 mg/kg/day, M/F), based on decreases in body weight, body weight gain, and food consumption, and differences in clinical chemistry and hematology parameters. The NOAEL is 500 ppm (equivalent to 33.2/41.2 mg/kg/day, M/F).

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.6200b; OECD 424) for a subchronic neurotoxicity study in the rat.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were presented in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: OPPTS 870.7485 [§85-1]; Metabolism Study in Rats

Work Assignment No. 6-1-229 U (MRID 47372509)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
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Prepared by
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Signature: Michael E Viana
Date: 11/25/09

Secondary Reviewer:
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Signature: David A. McEwen
Date: 11/25/09

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.
Signature: Michael E Viana
Date: 11/25/09

Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T.
Signature: Steven Brecher
Date: 11/25/09

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/23/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Lori Brunsman
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Metabolism - Rat; OPPTS 870.7485 [§85-1]; OECD 417.

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (RADIOCHEMICAL PURITY): Fluopyram (>98%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Klempner, A. (2008) [Phenyl-UL-^{14}C]-AE C656948: absorption, distribution, excretion, and metabolism in the rat. Bayer CropScience AG, Monheim, Germany. Study No.: M11819165. Report No.: MEF-07/508, M-298614-01, ASB2008-5536. Feb. 22, 2008. MRID 47372509. Unpublished

SPONSOR: Bayer CropScience, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a metabolism study (MRID 47372509), [phenyl-UL-^{14}C]-AE C656948 (Batch/Lot No. not provided; radiochemical purity >98%) in aqueous 0.5% Tragacanth was administered by oral gavage to groups of Wistar [Hsd/Cpb: WU] rats for the following experiments: (i) a single 5 mg/kg dose administered to five bile duct cannulated males; (ii) a single 5 mg/kg dose administered to four rats/sex; (iii) a single 250 mg/kg dose administered to four rats/sex; and (iv) 5 mg/kg doses of non-radiolabeled test material administered daily for 14 days to four males, followed by one dose of radiolabeled test material at 5 mg/kg. All animals were killed 168 hours after the final dose was administered except the bile duct-cannulated animals, which were terminated at 48 hours post-dosing. Metabolite profiles were determined for pooled urine, feces, and bile (where applicable) samples collected from all of the experimental groups.

[Phenyl-UL-^{14}C] -AE C656948 was rapidly absorbed from the gastrointestinal tract in all test groups. Absorption commenced immediately after oral dosing as shown by the plasma curves and the values calculated for the absorption half-lives (0.1 – 0.5 h). Based on the results obtained in bile duct cannulated male rats, the absorption rate accounted for more than 93%. The test material was widely distributed in the body with highest organ/tissue concentrations found in liver, kidney, erythrocytes and adrenals. In the experiments in non-cannulated rats, the majority of the administered dose had been excreted 168 h post dosing with fecal excretion accounting for 47%-64% and urinary excretion accounting for 35%-45% of the administered dose. Nonetheless, total residues in body (GIT excluded) were still found in the range between 2 and 6%. The high

values in the excretory organs liver and kidney suggest that excretion was still ongoing. Despite these observations, the experiment with repeated administration did not provide indications of a relevant potential for bioaccumulation since excretion and residues patterns were not altered. Considerable enterohepatic circulation was proven by high biliary (78.5% within 48 hours in males) and low renal excretion in the bile fistulation test.

The test compound was extensively metabolized, with a high number of metabolites occurring of which 9 to 22 could be structurally identified and quantified in the different groups and matrices. The ethyl linking group of the molecule was the preferred site for metabolism. The metabolic transformations detected were hydroxylation of the ethyl linking group of the parent compound forming AE C656948-7-hydroxy and 8-hydroxy metabolites. Further oxidation of AE C656948-7-hydroxy and 8-hydroxy metabolites resulted in AE C656948-enol which was further conjugated with glucuronic acid. Hydroxylation of the phenyl ring led to AE C656948-phenol and AE C656948-7-OH-phenol. All of the hydroxylated metabolites were conjugated mainly with glucuronic acid and, to a lower extent, with sulfate. The cleavage of the molecule yielded AE C656948-benzamide that was one of the most abundant metabolites. This molecule was further metabolized via oxidation, hydroxylation and conjugation to AE C656948-benzoic acid and various AE C656948-benzamide- and AE C656948-hydroxybenzamide-conjugates. The phenyl ring moiety was also conjugated with glutathione followed by further degradation to AE C656948-7-OH-methyl-sulfone, AE C656948-BA-methyl-sulfoxide, and AE C656948-BA-methyl-sulfone.

This study is classified **acceptable/guideline** and satisfies the requirements [OPPTS 870.7485, OECD 417] for a metabolism study in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: Non-Guideline; Organ Depletion Study in Rats

Work Assignment No. 6-1-229 X (MRID 47372510)

Prepared for
Health Effects Division
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Signature: David A. McEwen
Date: 11/25/09

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.
Signature: Michael E Viana
Date: 11/25/09

Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T.
Signature: Steven Brecher
Date: 11/25/09

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Lori Brunsman
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/'11

DATA EVALUATION RECORD

STUDY TYPE: Non-Guideline; Organ Depletion Study in Rats

PC CODE: 080302 **DP BARCODE:** D353273

TXR#: 0055218

TEST MATERIAL (RADIOCHEMICAL PURITY): Fluopyram (>99%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Koester, J. and Klempner, A. (2008) [Pyridyl-2,6-^{14}C]-AE C656948: metabolism in organs and tissues of male and female rats (3 timepoints). Bayer CropScience AG, Development Metabolism/Enviromental Fate, Germany. Report Nos.: MEF-08/115, M-298834-01, ASB2008-5541, March 03, 2007. MRID 47372510. Unpublished

SPONSOR: Bayer CropScience

EXECUTIVE SUMMARY: In a non-guideline study (MRID 47372510), [pyridyl-2,6-^{14}C]-AE C656948 (Batch/Lot No. not provided; radiochemical purity >99%) in aqueous 0.5% Tragacanth was administered by oral gavage to three groups of four Wistar [Hsd/Cpb: WU] rats/sex at a nominal doses of 5 mg/kg. Groups were terminated at 1, 4, or 24 hours post-dosing, and urine, feces, and plasma were collected. Radioactivity was measured in urine, plasma, carcass, kidneys, liver, gastrointestinal tract (with feces), skin, and perirenal fat. Metabolic profiles were determined for plasma, urine pools, and extracts of liver, kidney, and fat for each time point.

The overall recovery accounted for 97.2-98.8% of the administered dose in males and 97.8-99.7% of the administered dose in females. The majority of radioactivity was detected in the gastrointestinal tract (with feces) in the males at all time points; in females, the majority of radioactivity was detected in the body without the gastrointestinal tract at 1 hour post-dosing, then in the gastrointestinal tract (with feces) at 4 and 24 hours post-dosing.

The highest TRR (total radioactive residues) were detected in the organs and tissues as well as in the combined GIT plus faeces at one hour after administration. The distribution of the radioactivity within the central compartments of the body (e.g. blood, liver, and kidney) was fast and showed a distinctive preference towards the liver as the main organ responsible for metabolism and to a smaller extent to the kidney. Residues decreased significantly towards study

termination. In comparison to the male rats, the TRR values of organs and tissues from female rats were higher at nearly all points in time.

[Pyridyl-2,6-^{14}C]-AE C656948 was extensively metabolized and more than 20 metabolites were identified. Molecular cleavage occurred at least in a range of 23-34% of the administered dose in both sexes represented by numerous label-specific metabolites. In the various samples, some sex differences were observed with regard to the ratio of pyridyl label-specific and common metabolites which contained the intact molecular structure. The metabolic transformation of the parent compound was generally more pronounced in male rats. This was obvious from somewhat higher findings of unchanged parent compound in tissues of female rats compared to male rats. The metabolism of [pyridyl-2,6-^{14}C]-AE C656948 in male and female rats was principally oxidative and took place mainly at the ethylene bridge of the molecule. The metabolic transformations detected were hydroxylation of the ethyl linking group of the parent compound forming AE C656948-7-hydroxy and -8-hydroxy metabolites and one di-hydroxylated metabolite. Hydroxylation of the phenyl ring of AE C656948 led to AE C656948-phenol and -7-OH-phenol. Hydrolytic cleavage led to AE C656948-pyridyl-hydroxyethyl and -pyridyl-carboxylic acid (PCA). Subsequent oxidation of AE C656948-pyridyl-hydroxyethyl led to mainly AE C656948-pyridyl-acetic acid (PAA) and to a lesser extent to AE C656948-ethyl-diol, and -hydroxy-PAA. Elimination of water from compounds hydroxylated in the ethylene bridge afforded the AE C656948-Z-olefine and E-olefine (E- and Z-olefine can isomerise into each other). As the double bond of the olefine may be a target for epoxidation and a dihydroxy-metabolite which could result from hydrolysis of an epoxid by epoxid hydroxylase was observed, the olefine was considered to be of potential toxicological relevance. Several hydroxylated metabolites were conjugated with glucuronic acid and, to a lesser extent, with sulfate.

This study is classified **acceptable/non-guideline** and provides information regarding the distribution, excretion, and metabolism of the test compound following oral dosing in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: OPPTS 870.7485 [§85-1]; Metabolism Study in Rats

Work Assignment No. 6-1-229 V (MRID 47372511)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
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Prepared by
Pesticides Health Effects Group
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Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/25/09*
Secondary Reviewer: David A. McEwen, B.S.	Signature: David A. McEwen Date: *11/25/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/25/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Date: *11/25/09*

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:** [signature]
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/22/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** [signature]
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11

DATA EVALUATION RECORD

STUDY TYPE: Metabolism - Rat; OPPTS 870.7485 [§85-1]; OECD 417.

PC CODE: 080302 **DP BARCODE:** D353273

TXR#: 0055218

TEST MATERIAL (RADIOCHEMICAL PURITY): Fluopyram (>99%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Klempner, A. (2008) [Pyridyl-2,6-^{14}C]-AE C656948: absorption, distribution, excretion, and metabolism in the rat. Bayer CropScience AG, Development Metabolism/Enviromental Fate, Germany. Study No.: M31819167: Report Nos.: MEF-07/486, M-298924-01, ASB2008-5537. March 03, 2008. MRID 47372511. Unpublished

SPONSOR: Bayer CropScience

EXECUTIVE SUMMARY: In a metabolism study (MRID 47372511), [pyridyl-2,6-^{14}C]-AE C656948 (Batch/Lot No. not provided; radiochemical purity >99%) in aqueous 0.5% Tragacanth was administered by oral gavage to groups of Wistar [Hsd/Cpb: WU] rats for the following two experiments: a single 5 mg/kg dose administered to six bile duct cannulated males; and a single 5 mg/kg dose administered to four rats/sex. All animals were killed 168 hours after the final dose was administered except the bile duct-cannulated animals, which were terminated at 48 hours post-dosing. Metabolite profiles were determined for pooled urine, feces, and bile (where applicable) samples collected from all of the experimental groups.

[Pyridyl-2,6-^{14}C]-AE C656948 was rapidly absorbed from the gastrointestinal tract in all test groups. The absorption commenced immediately after oral dosing as shown by the plasma curves and the values calculated for the absorption half-lives (0.3 – 0.4 h). Based on the results obtained in bile duct cannulated male rats, the absorption rate accounted for 97.7 % of the recovered radioactivity and, thus, the administered dose may be considered to be virtually completely absorbed and systemically bioavailable.

The test material was widely distributed in the body with highest organ/tissue concentrations found in liver and erythrocytes.

Excretion was almost completed 72 h after administration. At this time, males and females had excreted more than 98 % of the administered dose via urine and feces with some minor sex-related differences. In bile duct-cannulated male rats, the major part of radioactivity (86.8 %) was eliminated via bile proving, together with the low renal excretion in the bile fistulation experiment, the significant enterohepatic circulation of this compound. At 168 h after oral administration, residues in most of the organs and tissues of male and females rats were very low (<0.1 % of the dose) and, thus, retention or accumulation of AE C656948 or its metabolites are not expected.

Metabolism was extensive with up to 25 metabolites in the different groups and matrices that could be identified and quantified. The ethyl linking group of the molecule was the preferred site for metabolism. The metabolic transformations detected were hydroxylation of the ethyl linking group of the parent compound forming AE C656948-7-hydroxy and -8-hydroxy metabolites. Further oxidation of AE C656948-7-hydroxy and 8-hydroxy metabolites resulted in AE C656948-enol, which was conjugated with glucuronic acid. Hydroxylation of the phenyl ring of AE C656948 led to AE C656948-phenol and AE C656948-7-OH-phenol. All of the hydroxylated metabolites were conjugated mainly with glucuronic acid and, to a lesser extent, with sulfate. Hydrolytic cleavage and subsequent oxidation mainly led to AE C656948-pyridyl-acetic acid (PAA), AE C656948-ethyl-diol, and -pyridyl-carboxylic acid (PCA).

This study is classified **acceptable/guideline** and satisfies the requirements [OPPTS 870.7485, OECD 417] for a metabolism study in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: Non-Guideline; Autoradiographic Study in Rats

Work Assignment No. 6-1-229 W (MRID 47372512)

Prepared for
Health Effects Division
Office of Pesticide Programs
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Secondary Reviewer: David A. McEwen, B.S.	Signature: David A. McEwen Date: *11/25/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/25/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Date: *11/25/09*

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:** [signature]
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** [signature]
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/'11

DATA EVALUATION RECORD

STUDY TYPE: Non-Guideline; Autoradiographic Study in Rats

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (RADIOCHEMICAL PURITY): Fluopyram (>98%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Koester, J. (2008) [Pyridyl-2,6-^{14}C]-AE C656948: distribution of the total radioactivity in male and females rats determined by quantitative whole body autoradiography (QWBA), determination of the exhaled $^{14}CO_2$, and metabolic profiling in excreta. Bayer CropScience AG, Development Metabolism/ Enviromental Fate, Germany. Report No.: MEF-07/457, M-296485-01, ASB2008-5540. Study No.: M1819149-3. Jan. 15, 2008. MRID 47372512. Unpublished

SPONSOR: Bayer CropScience

EXECUTIVE SUMMARY: In a non-guideline study (MRID 47372512), [pyridyl-2,6-^{14}C]-AE C656948 (Batch/Lot No. not provided; radiochemical purity >98%) in aqueous 0.5% Tragacanth was administered by oral gavage to eight Wistar [Hsd/Cpb: WU] rats/sex at nominal doses of 3 mg/kg in males and 4.3 mg/kg in females. Urine and feces were collected at regular intervals up to 168 hours post-dosing. Carbon dioxide and other volatiles from expired air were trapped and sampled at 24 and 48 hours post-dosing. The distribution of total radioactivity in organs and tissues was determined at regular intervals by means of quantitative whole-body autoradiography. Groups of one male and one female each were killed at 1, 4, 8, 24, 48, 72, 120, and 168 hours post-dosing. The animals were fixed in a stretched position and immediately frozen at approximately -70°C. The frozen carcass was then embedded in a slurry of carboxymethylcellulose (7-8%), and the slurry was deep frozen. Sections were then cut from the block using a microtome; the sections were attached to adhesive tape and freeze-dried overnight. Four sections from each animal showing the relevant organs and tissues were exposed using imaging plates, and the exposed plates were scanned. A control animal of each sex was similarly dosed, and prepared as above four hours post-dosing to correct for possible chemographic effects.

The distribution and elimination of radioactivity in males and females was very similar. In both sexes, [pyridyl-2,6-^{14}C]- AE C656948 was readily absorbed from the gastrointestinal tract and distributed to almost all organs and tissues.

The excretion of radioactivity amounted to 51-54% in the urine and 43-54% in the feces. About three days after dosage, the urinary and fecal excretion was nearly completed. Only a very minor portion of the dose was excreted in the time range between 72 and 168 h after administration. Less than 1% of the administered dose was expired in both sexes, thus demonstrating the stability of the ^{14}C-phenyl labeling position. Generally, maximum equivalent concentrations for the organs and tissues were reached within one hour post-dosing, except for kidney and perirenal fat in the females which peaked after 4 hours.

In males, most organs of the central compartment (e.g. liver, kidney), and some peripheral tissues such as fat, some glands (e.g. adrenal, thyroid, Harderian), and nasal mucosa, concentrations were higher than in blood at t_{max} and for liver also at $t_{168\ h}$ suggesting a rapid clearance of test item related radioactivity from blood and distribution to these organs and tissues. For the high liver value at $t_{168\ h}$, a still ongoing degradation on a high level was assumed. The equivalent concentrations in blood and all organs and tissues declined up to the end of the study. The highest value was detected in the nasal mucosa (6.1% of the maximum equivalent concentration).

In females, most organs of the central compartment (e.g. liver, kidney) and some peripheral tissues such as fat, brain, some glands (e.g. adrenal, thyroid, preputialis, Harderian) and nasal mucosa, concentrations were higher than in blood at the times of t_{max} and for liver, nasal mucosa, Harderian gland and glandula preputialis also at $t_{168\ h}$. Similar to the males, the absorbed radioactivity was rapidly cleared from blood and distributed to organs and tissues of the animals. The higher values for the mentioned organs at $t_{168\ h}$ indicated a still ongoing degradation on a high level in the liver and additionally a delayed depletion of test compound related radioactivity from the other organs. The equivalent concentrations in blood and all organs and tissues declined up to the end of the study. The highest value was detected in the nasal mucosa (4.9% of the maximum equivalent concentration).

This study is classified **acceptable/non-guideline** and provides information regarding the distribution and excretion of the test compound following oral dosing in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: Non-Guideline; Autoradiographic Study in Rats

Work Assignment No. 6-1-229 DD (MRID 47372513)

Prepared for
Health Effects Division
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Date: 11/25/09

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.
Signature: Michael E Viana
Date: 11/25/09

Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T.
Signature: Steven Brecher
Date: 11/25/09

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/22/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11

DATA EVALUATION RECORD

STUDY TYPE: Non-Guideline; Autoradiographic Study in Rats

PC CODE: 080302 **DP BARCODE:** D353273

TXR#: 0055218

TEST MATERIAL (RADIOCHEMICAL PURITY): Fluopyram (>98%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Koester, J. (2008) [Phenyl-UL-^{14}C]-AE C656948: distribution of the total radioactivity in male and females rats determined by quantitative whole body autoradiography (QWBA), determination of the exhaled $^{14}CO_2$, and metabolic profiling in excreta. Bayer CropScience AG, Development Metabolism/ Enviromental Fate, Germany. Report Nos.: MEF-07/456, M-296623-01, ASB2008-5539. Study No.: M1811509-5. Jan. 15, 2008. MRID 47372513. Unpublished

SPONSOR: Bayer CropScience

EXECUTIVE SUMMARY: In a non-guideline study (MRID 47372513), [phenyl-UL-^{14}C]-AE C656948 (Batch/Lot No. not provided; radiochemical purity >98%) in aqueous 0.5% Tragacanth was administered by oral gavage to eight Wistar [Hsd/Cpb: WU] rats/sex at a nominal dose of 3 mg/kg. Urine and feces were collected at regular intervals up to 168 hours post-dosing. Carbon dioxide and other volatiles from expired air were trapped and sampled at 24 and 48 hours post-dosing. The distribution of total radioactivity in organs and tissues was determined at regular intervals by means of quantitative whole-body autoradiography. Groups of one male and one female each were killed at 1, 4, 8, 24, 48, 72, 120, and 168 hours post-dosing. The animals were fixed in a stretched position and immediately frozen at approximately -70°C. The frozen carcass was then embedded in a slurry of carboxymethylcellulose (7-8%), and the slurry was deep frozen. Sections were then cut from the block using a microtome; the sections were attached to adhesive tape and freeze-dried overnight. Four sections from each animal showing the relevant organs and tissues were exposed using imaging plates, and the exposed plates were scanned. A control animal of each sex was similarly dosed, and prepared as above four hours post-dosing to correct for possible chemographic effects.

The distribution and elimination of radioactivity in males and females was very similar. In both

sexes, [phenyl-UL-^{14}C]- AE C656948 was readily absorbed from the gastrointestinal tract and distributed to almost all organs and tissues. The major part of the dosed radioactivity (53-65%) was excreted with feces; 32-41% was excreted via the urine. After 72 hours, the fecal excretion was nearly completed. In the males, only a very minor part of the dose was excreted between 72 and 168 hours after dosing. In both sexes, the urinary excretion showed a slightly different behavior, as a clear plateau level was not reached during the sampling period of seven days and renal excretion was still ongoing on a low level. Less than 0.07-0.09% of the administered dose was expired, demonstrating the stability of the ^{14}C-phenyl labelling position. For nearly all organs and tissues, the highest concentration equivalents (CEQ_{max}) were reached during the first day after administration. In females, the CEQ_{max} for the nasal mucosa and glandula preputialis peaked after 48 hours. For most organs of the central compartment (e.g. liver, kidney) as well as peripheral tissues such as fat, muscle, some glands (e.g. adrenal, thyroid, Harderian) and nasal mucosa, the CEQ_{max} was higher than in blood at the times of t_{max} and $t_{168\ h}$ suggesting a rapid clearance from blood and distribution to organs and tissues of the animals. In the females, the higher values for the organs at $t_{168\ h}$ indicate a still ongoing degradation (liver) and excretion (kidney) and a delayed depletion of test compound related radioactivity from the other organs. The equivalent concentrations in blood and all organs and tissues declined up to the end of the study (168 h post-dosing). In males, the highest value was detected in the nasal mucosa (52.1% of the maximum equivalent concentration). In females, the highest values were detected in the glandula preputialis (24% of the maximum equivalent concentration) and in the nasal mucosa (55%). In both sexes, the lowest was in the pineal body.

This study is classified **acceptable/non-guideline** and provides information regarding the distribution and excretion of the test compound following oral dosing in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.

EPA Reviewer: Whang Phang, PhD **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
Secondary Reviewe: Myron Ottley, Ph.D. **Signature:** Myron Ottley
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11

DATA EVALUATION RECORD

STUDY TYPES: In vitro dermal absorption sty using human and rat skin

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0054868

TEST MATERIAL (PURITY): AE C656948 in a SC 500 formulation

SYNONYMS: 5-Ethyl-5-phenyl-2,4,6-(1H,3H,5H)-pyrimidinetrione

CITATION: Blanck, M. (2007): AE C656948: Comparative in vitro dermal absorption study in SC 500 formulation using human and rat skin. Bayer CropScience, Sophia Antipolis Cedex, France. SA 07123, M-295237-01, ASB2008-5188. Nov. 30, 2007. MRID 47372514. Unpublished

SPONSOR: Bayer CropScience, Alfred Nobel Str. 50, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In an *in vitro* dermal absorption study (MRID 47372514) where dermatomed rat and human skin membranes maintained in flow through diffusion cells at approximately 32°C. The dematomed skin membranes were exposed to [^{14}C]-AC C56948 at two concentrations: one was a neat formulation (500 mg AE C656 948/ml formulation) and the other was the spray dilution (0.5 mg AE C656948/ml formulation). The two formulations were applied at a rate of 10 µL/cm^2 to the mounted skin samples. Receptor fluid samples were collected at hourly interval for the duration of the study (24 hours). Eight hours post-application, epidermal membranes were washed. At the end of the study, the skin samples were swabbed and tape-stripped to remove residual test material from the skin surface.

The results demonstrated the recovery to be 100.7% to 103.1% of the applied concentration for both high and low concentrations. For the **neat formulation**, majority of the radioactivity was found in the skin swab (100.9% & 100.1% of the applied concentration in human skin and rat skin, respectively) and tap-stripes (0.707% and 0.728% of the applied concentrations for human and rats skin). The percentages of the test material found in the receptor fluid from 0-24 hours were 0.004% and 0.077% of the applied concentrations for human and rat skin, respectively. For the spray dilution, The mean percentages of the applied concentrations considered to be potentially absorbable (directly absorbed plus remaining at the application site) were 0.101% and 2.097% for human skin and rat skin, respectively. The results of the neat formation experiment yielded a factor of difference of 21 between human and rat skin.

For the **spray dilution,** the majority of the applied radioactivity was again found in the skin swab (97.6% and 86.2% of the applied concentrations in human and rat skin swabs, respectively), and tap-stripes contained 1.12% and 2.33% of the applied concentrations in human and rat skin,

respectively. The percentages of the test material found in the receptor fluid from 0-24 hours were 1.23% and 8.56% of the applied concentrations for human and rat skin, respectively. The mean percentages of the applied concentrations considered to be potentially absorbable (directly absorbed plus remaining at the application site) were 1.77% and 12.43% for human skin and rat skin, respectively. The results of spray dilution experiment showed that there was a factor of difference of 7 between human and skin.

This study is considered **acceptable** and provides information regarding in vitro dermal absorption of fluopyram.

COMPLIANCE: A GLP Compliance statement was signed and included in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: Non-Guideline; 28-Day Range-Finding Oral Toxicity Study in Dogs

Work Assignment No. 6-1-229 C (MRID 47372515)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Building 100, Suite B
Durham, NC 27713

Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/10/09*
Secondary Reviewer: John W. Allran, M.S.	Signature: Date: *11/10/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/10/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Date: *11/10/09*

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel

EPA Reviewer: Whang Phang **Signature:** [signature]
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/20/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** [signature]
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11

DATA EVALUATION RECORD

STUDY TYPES: Non-Guideline; 28-Day Range-Finding Oral (Gavage) Toxicity Study in Dogs

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (99.0%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Kennel, P. (2004) AE C656948: preliminary 28-day toxicity study in the dog by gavage. Bayer CropScience, Sophia Antipolis Cedex, France. Laboratory Report Nos.: SA 04049, M-242097-01, ASB2008-5507. Dec. 13, 2004. MRID 47372515. Unpublished

SPONSOR: Bayer CropScience, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a range-finding oral toxicity study (MRID 47372515), fluopyram (99.0% a.i., Lot/Batch PFI 0304) in aqueous 0.4% methylcellulose 400 was administered by daily oral gavage (5 mL/kg) to two beagle dogs/sex/dose group at dose levels of 0, 30, 150, or 750 mg/kg/day for at least 28 days. Mortality, clinical signs of toxicity, body weights, and food consumption were recorded at regular intervals. Ophthalmoscopic examinations, hematology and clinical chemistry measurements, and urinalysis were performed prior to administration of the test compound and approximately at the end of treatment. On Days 29 and 30, all animals were euthanized and subjected to a gross necropsy. Histopathological examinations were also performed (organs/tissues not specified).

There were no effects of treatment on mortality, clinical signs, body weights, body weight gains, food consumption, ophthalmoscopic examinations, or urinalysis.

At 750 mg/kg/day, diffuse centrilobular to panlobular hepatocellular hypertrophy was observed in 2/2 males (minimal to slight severity) and 2/2 females (slight severity), and focal/multifocal eosinophilic inclusion bodies were noted in 1/2 males (minimal severity) and 2/2 females (minimal to slight severity). Additionally at this dose, it was stated that the two males demonstrated decreased erythrocyte counts, hemoglobin, and hematocrit, and a high alkaline phosphatase activity was observed in one male and one female. The female also exhibited high

gamma-glutamyltransferase activity and increased triglycerides. It was further stated that absolute and relative (to body) liver weights were clearly increased in both sexes at 750 mg/kg/day. As no data regarding the magnitude of these changes were presented, the reviewers cannot be certain as to the severity and adverse nature of these findings.

At 150 mg/kg/day and below, the only finding reported was a slight increase in liver weights in both sexes at 150 mg/kg/day and in males at 30 mg/kg/day. This finding was considered to be an adaptive response of the liver to exposure to the test compound.

The LOAEL is 750 mg/kg/day, based on liver toxicity as described above in both sexes, and hematology findings in males. The NOAEL is 150 mg/kg/day.

This study is classified **acceptable/non-guideline** and provides sufficient data to aid in dose level selection for the definitive subchronic oral toxicity study in dogs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality Statements were included in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: Non-Guideline; 28-Day Range-Finding Oral Toxicity Study in Rats

Work Assignment No. 6-1-229 A (MRID 47372516)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Building 100, Suite B
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Primary Reviewer:
Michael E. Viana, Ph.D., D.A.B.T.
Signature: Michael E Viana
Date: *11/10/09*

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John W. Allran, M.S.
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Date: *11/10/09*

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Date: *11/10/09*

Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T.
Signature: Steven Brecher
Date: *11/10/09*

Disclaimer

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EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/24/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Lori Brunsman
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPES: Non-Guideline; 28-Day Range-Finding Oral (Dietary) Toxicity Study in Rats

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (98.6%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Kennel, P. (2004) AE C656948: exploratory 28-day toxicity study in the rat by dietary administration. Bayer CropScience, Sophis Antipolis Cedex, France. Laboratory Report Nos.: SA 03332, M-085510-01, ASB2008-5503; June 8, 2004. MRID 47372516. Unpublished

SPONSOR: Bayer CropScience, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a range-finding oral toxicity study (MRID 47372516), fluopyram (98.6% a.i., Lot/Batch FLH 999) was administered in the diet to five Wistar (Rj:WI [IOPS HAN]) rats/sex/dose group at dose levels of 0, 50, 400, or 3200 ppm (equivalent to 0/0, 4.0/4.6, 31.0/36.1, and 254/263 mg/kg/day in males/females) for 28 days. Mortality, clinical signs of toxicity, body weights, and food consumption were recorded at regular intervals. On Day 29, blood samples were collected for measurement of hematology and clinical chemistry parameters, and all animals were then subjected to a gross necropsy. Histopathological examinations were performed on the adrenal gland, brain, liver, kidney, lung, ovary, pituitary, spleen, testis, and thyroid (with parathyroid). Additionally, microsomal preparations were made from the livers of all rats and analyzed for total cytochrome P-450 content and activities of ethoxyresorufin-O-deethylase (EROD), benzoxyresorufin-O-dealkylase (BROD), and pentoxyresorufin-O-deethylase (PROD).

All animals survived to scheduled termination. There were no effects of treatment on clinical signs.

Treatment-related systemic effects were observed at 3200 ppm. Body weight gains were decreased by 12-28% in males (Weeks 1 and 3) and by 16-29% in females (Weeks 1, 3, and 4). Additionally in the females, overall body weight gains were decreased by 14%, and food consumption was reduced by 4-10% throughout the study.

Liver toxicity was noted at 3200 ppm. Absolute and relative (to body) liver weights were each increased by 54% in males, and by 65% and 73%, respectively, in females. These weight increases were associated with enlarged and dark livers at necropsy, and minimal to moderate centrilobular hepatocellular hypertrophy in most animals in both sexes. Total cytochrome P-450 levels were increased by 37% and 41% in males and females, respectively, with increases in BROD (1831% in males, 3002% in females) and PROD (941% males, 1526% in females). Males exhibited a 30% increase in platelet count and increased prothrombin time (18.0 s treated vs. 13.4 s controls), and total cholesterol and triglycerides were increased in males (82% and 148%, respectively) and females (84% and 152%, respectively).

Also at 3200 ppm, absolute and relative thyroid weights were increased by 43% and 41%, respectively, in males, with hypertrophy of the follicular cells noted in 3/5 males.

At 400 ppm, absolute and relative liver weights were increased by 12% and 7%, respectively, in males, and by 16% and 15%, respectively, in females. These changes were not statistically significant. Goss examination showed enlarged and dark livers, and histological evaluation revealed centrilobular hepatocellular hypertrophy. However, the magnitude, incidence, and severity were lower than those observed at 3200 ppm. Total cytochrome P-450 levels were increased by 20% and 15% in males and females, respectively, with increases in BROD (698% in males, 842% in females) and PROD (350% in males, 360% in females). The liver effects at 400 ppm were considered as an adaptive response of the liver to the exposure of the test compound and were not adverse.

Increased absolute and relative kidney weights were observed in the 400 ppm and above males (19-20% absolute weight; 15-18% relative weight). These increased weights were associated with microscopic changes of hyaline droplet nephropathy (basophilic tubules, hyaline droplets in the proximal tubule, and granular casts in the medulla). This nephropathy was considered to be due to accumulation of $\alpha_{2\mu}$-globulin, a common toxicological finding in young male rats following exposure to toxicants. Therefore, this finding was not considered relevant to human health considerations.

The LOAEL is 3200 ppm (equivalent to 254/263 mg/kg/day in males/females), based on decreased body weight gains and liver toxicity as described above in both sexes, increased thyroid weights and hypertrophy of the follicular cells in males, and decreased overall body weight gains and food consumption in females. The NOAEL is 400 ppm (equivalent to 31.0/36.1 mg/kg/day in males/females).

This study is classified **acceptable/non-guideline**. Although it satisfies the majority of the requirements for a repeated dose 28-day oral toxicity study in rodents (OPPTS 870.3050; OECD 407), it was stated that as a range-finding study, it was not intended to meet guideline requirements.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality Statements were included in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: Non-Guideline; 28-Day Range-Finding Oral Toxicity Study in Mice

Work Assignment No. 6-1-229 B (MRID 47372517)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
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Primary Reviewer:
Michael E. Viana, Ph.D., D.A.B.T.

Signature: Michael E Viana
Date: *11/10/09*

Secondary Reviewer:
John W. Allran, M.S.

Signature: John W Allran
Date: *11/10/09*

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.

Signature: Michael E Viana
Date: *11/10/09*

Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T.

Signature: Steven Brecher
Date: *11/10/09*

Disclaimer

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EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/29/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Lori Brunsman
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPES: Non-Guideline; 28-Day Range-Finding Oral (Dietary) Toxicity Study in Mice

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (99.4%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Kennel, P. (2004) AE C656948: preliminary 28-day toxicity study in the mouse by dietary administration. Bayer CropScience, Sophia Antipolis Cedex, France . Laboratory Report Nos.: SA 04013, M-088486-01, ASB2008-5506, Sept. 02, 2004. MRID 47372517. Unpublished

SPONSOR: Bayer CropScience, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a range-finding oral toxicity study (MRID 47372517), fluopyram (99.4% a.i., Lot/Batch FLH 1046) was administered in the diet to five C57BL/6J mice/sex/dose group at dose levels of 0, 150, 1000, or 5000 ppm (equivalent to 0/0, 24.7/31.1, 162/197, and 747/954 mg/kg/day in males/females) for 28 days. Mortality, clinical signs of toxicity, body weights, and food consumption were recorded at regular intervals. On Day 29, blood samples were collected for measurement of clinical chemistry parameters, and all animals were then subjected to a gross necropsy. Histopathological examinations were performed on the adrenal gland, liver, kidney, lung, ovary, spleen, testis, and thyroid (with parathyroid).

At 5000 ppm, the **maximum tolerated dose** was exceeded. All males and 3/5 females were euthanized between Days 17 and 27. These animals were observed with reduced motor activity, hunched posture, piloerection, wasted appearance, and/or coldness to the touch in both sexes, with labored respiration in 3/5 males and distended abdomen in 2/3 females, noted mainly on the day of euthanasia or for a few days prior. A loss of body weight and reduced food intake accompanied these signs. At necropsy, a pale pancreas was observed in all males and in 2/3 females. Rounded borders were observed in the liver in 3/5 males and 1/3 females. Dark liver was observed in 4/5 males and all females; enlarged liver was observed in 1/5 males and 2/3 females. Thymus size was clearly reduced in 4/5 males and 1/3 females and distended abdomen was noted in 3/5 males. Red liquid was noted in the thoracic cavity in all males. Treatment-related effects were seen in the adrenal glands, liver, lungs, spleen, thymus, and thyroid gland.

Hypertrophy, vacuolation, and degeneration/necrosis of the zona fasciculata were seen in the adrenal glands in all animals, together with perivascular and intra-alveolar hemorrhage and degeneration/inflammation of pulmonary veins in the lungs and erythroid extramedullary hematopoiesis in the spleen. Focal hemorrhage was seen in the thyroid gland in 3/5 males, and decreased cellularity of the cortex and focal hemorrhage were seen in the thymus in all animals where examination was possible. In the liver, hypertrophy of hepatocytes (mainly centrilobular), hepatocellular eosinophilia, bile duct/oval cell hyperplasia, focal necrosis and single hepatocellular necrosis were seen in all animals, and centrilobular degeneration/necrosis in 1/5 males. It was considered that premature sacrifice in all males and 1/3 females was associated with intrathoracic hemorrhage, as the majority of the decedents had areas of hemorrhage in the thoracic cavity, thyroid gland, lungs, and thymus.

In the two surviving females dosed at 5000 ppm, distended abdomen was noted between Days 8 and 10 in one animal. Body weights, body weight gains, and food consumption were similar to controls. Total cholesterol was increased by 118%, total protein was increased by 16%, and alanine aminotransferase was increased by 384%. Absolute and relative (to body) liver weights were increased by 132-144%. Enlarged liver was observed in both females; dark liver was noted in 1/2 females. Hypertrophy of the zona fasciculata was seen in the adrenal glands in both females. The following microscopic findings were noted in the liver of both females: moderate hypertrophy of centrilobular hepatocytes, slight focal necrosis, minimal hepatocellular eosinophilia, and minimal bile duct/oval cell hyperplasia. Additionally, minimal single cell hepatocellular necrosis was observed in 1/2 females.

At 1000 ppm and below, there were no effects of treatment on mortality, clinical signs, body weights, body weight gains, or food consumption.

Liver toxicity was noted at 1000 ppm. Alanine aminotransferase was increased by 259% in males. Absolute and relative liver weights were increased by 41-46% in males, and by 27-38% in females. Enlarged liver was observed in all males and 4/5 females; dark liver was noted in 3/5 males and 2/5 females. The following microscopic findings were noted: hypertrophy of centrilobular hepatocytes in 5/5 males (moderate severity) and 5/5 females (minimal to slight severity); minimal single cell hepatocellular necrosis in 5/5 males; minimal focal necrosis in 3/5 males and 2/5 females; and minimal bile duct/oval cell hyperplasia in 1/5 females.

Additionally at 1000 ppm, hypertrophy of the zona fasciculata was seen in the adrenal glands of 3/5 females.

The following findings were observed at 150 ppm. Absolute and relative liver weights were increased by 18-21% in males and 16-17% in females, and hypertrophy of centrilobular hepatocytes was noted in 5/5 males (minimal to slight severity) and 2/5 females (minimal severity). These minor findings were considered to represent an adaptive change of the liver to exposure to the test compound, and were not considered adverse.

The LOAEL is 1000 ppm (equivalent to 162/197 mg/kg/day in males/females), based on liver toxicity as described above in both sexes, and microscopic findings in the adrenal

glands in females. The NOAEL is 150 ppm (equivalent to 24.7/31.1 mg/kg/day in males/females).

This study is classified **acceptable/non-guideline**. Although it satisfies the majority of the requirements for a repeated dose 28-day oral toxicity study in rodents (OPPTS 870.3050; OECD 407), it was stated that as a range-finding study, it was not intended to meet guideline requirements.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality Statements were included in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: Non-Guideline; *In-Vitro* Study on Porcine Thyroid Peroxidase

Work Assignment No. 6-1-229 CC (MRID 47372518)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Building 100, Suite B
Durham, NC 27713

Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/25/09*
Secondary Reviewer: David A. McEwen, B.S.	Signature: David A. McEwen Date: *11/25/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/25/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Steven Brecher Date: *11/25/09*

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPES: *In-Vitro* Study on Porcine Thyroid Peroxidase; Non-Guideline

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.7%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Freyberger, A. (2008) AE C656948 (Fluopyram): *in-vitro* studies on the potential interactions with thyroid peroxidase-catalyzed reactions. Bayer HealthCare AG, PH- GDD Toxicology, Germany. Report No.: AT04481; M-299276-01, ASB2008-5443; March 5, 2008. MRID 47372518. Unpublished

SPONSOR: J. C. Garcin, Bayer CropScience SPR, Sophis Antipolis, France

EXECUTIVE SUMMARY: In a non-guideline study (MRID 47372518), the interactions of AE C656948 (94.7% a.i., Lot/Batch 08528/0002) in dimethyl sulfoxide with thyroid peroxidase-catalyzed reactions were investigated *in-vitro* using solubilized pig thyroid microsomes as an enzyme source. Guaiacol oxidation was used as a measure for peroxidase activity. Incubations were carried out using guaiacol, pig thyroid microsomes, hydrogen peroxide, and the test compound at final concentrations of 0, 3, 30, and 300 µM. Amitrole served as a positive control, and was used at 1.0 µM. Thyroid peroxidase-catalyzed iodine formation was also examined by replacing quaiacol with potassium iodide and using the same concentrations of the test compound as before. Amitrole (1.0 µM) and ethylenethiourea (5.0 µM) served as positive controls.

The test compound did not inhibit the thyroid peroxidase-catalyzed oxidation of guaiacol at concentrations up to 300 µM. Amitrole, the positive control, at a concentration of 1.0 µM inhibited thyroid peroxidase-catalyzed oxidation of guaiacol by 55%.

Similarly, the test compound did not inhibit thyroid peroxidase-catalyzed iodine formation at concentrations up to 300 µM. Ethylenethiourea, a trap of the iodinating intermediate, temporarily suppressed iodine formation. Amitrole at 1.0 µM inhibited the initial rate of this reaction by approximately 50%.

These findings suggest that the test compound does not affect thyroid hormone synthesis at the level of thyroid peroxidase.

This study is considered **acceptable/non-guideline** and provides information regarding the effects of the test compound on thyroid peroxidase and thyroid hormone synthesis.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

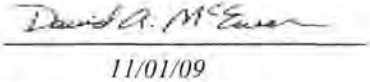
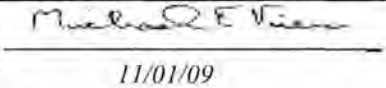
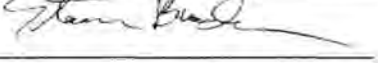
FLUOPYRAM

Study Type: Non-Guideline: 14-Day Mechanistic Study in Mice

Work Assignment No. 6-1-229 AA (MRID 47372519)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Building 100, Suite B
Durham, NC 27713

Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature:  Date: *11/01/09*
Secondary Reviewer: David A. McEwen, B.S.	Signature:  Date: *11/01/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature:  Date: *11/01/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature:  Date: *11/01/09*

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Stephen Brunsman
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11

DATA EVALUATION RECORD

STUDY TYPES: 14-Day Mechanistic Study in Mice; Non-Guideline

PC CODE: 080302

DP BARCODE: D353273

TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.7%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Rouquie, D. (2008) AE C656948: mechanistic 14-day toxicity study in the mouse by dietary administration (hepatotoxicity and thyroid hormone investigations). Bayer CropScience, Sophis Antipolis Cedex, France. Report Nos.: SA 07215, M-299522-01, ASB2008-5444. March 31, 2008. MRID 47372519. Unpublished

SPONSOR: Bayer CropScience, Alfred Nobel Str. 50, 40789 Monheim, Germany.

EXECUTIVE SUMMARY: In a non-guideline, mechanistic study (MRID 47372519), AE C656948 (94.7% a.i., Lot/Batch 08528/0002) was administered in the diet to groups of 15 male C57BL/6J mice/dose group at dose levels of 0 or 2000 ppm (equivalent to 0 and 311 mg/kg day) for either three or fourteen days. The rats were observed regularly for changes in mortality, clinical signs of toxicity, body weight, and food consumption. On the days of necropsy (Days 4 or 15), blood samples were taken from all animals for determination of TSH, T3, and T4 hormone levels. The mice were then exsanguinated and necropsied. Brain and liver were weighed, and pieces of the left and medial lobes of the liver from five mice/group were removed and fixed in neutral buffered 10% formalin. The remaining portions of the liver from these mice and the whole livers from the other ten males from each group were pooled (two whole livers pooled with one remaining portion) to generate five liver samples. Microsomal preparations were made from these five pooled samples and analyzed for total cytochrome P-450 content and activities of ethoxyresorufin-O-deethylase (EROD), benzoxyresorufin-O-dealkylase (BROD), pentoxyresorufin-O-deethylase (PROD), and UDP-glucuronosyltransferase (UDPGT).

No mortalities were observed, and there were no clinical signs of toxicity. Body weights and body weight gains were unaffected by treatment. There was a slight decrease in food consumption noted in the 3-day treatment group (decr. 12.5%) and in the 14-day treatment group

after 1 week of exposure (decr. 5.1%). T4 levels were decreased by 30% after 3 days and by 27% after 14 days of treatment; TSH levels were increased by 18% after 3 days and by 7% after 14 days of treatment. These results were consistent with the known feedback regulation mechanism of thyroid hormone homeostasis. No relevant changes in gross or microscopic pathology were observed in the thyroid gland.

Absolute and relative (to body) liver weights were increased by 59-61% at Days 4 and 15. The weight increases were associated with enlarged and/or dark livers observed at necropsy, and centrilobular to panlobular hepatocellular hypertrophy observed microscopically in all treated males (5/5 mice at Days 4 and 15). Additionally, an increased number of mitoses was observed in 5/5 males on Day 4, and single cell necrosis was noted in 4/5 males on Day 15. Total cytochrome P-450 content was increased by 71-116%, EROD activity was increased by 165-235%, PROD activity was increased by 2163-2890%, and BROD activity was increased by 8717-9061% on Days 4 and 15. In contrast, UDPGT activity was unaffected by treatment.

AE C656948 demonstrated the ability to induce total cytochrome P-450, PROD, BROD, and EROD activities in mouse liver after 3 and/or 14 days of dietary exposure at the high dose level of 2000 ppm. Hepatotoxicity became further apparent by liver weight increases and concomitant histological lesions. Rapid onset of these changes was noted in the 3-day experimental group. Furthermore, exposure to the test compound resulted in disturbance of thyroid hormone balance in male mice by causing a decrease in T4 levels with a concomitant increase in TSH. However, there were no microscopic findings of thyroid toxicity, perhaps due to the relatively short exposure period.

This study is considered **acceptable/non-guideline** and provides information regarding the effects of dietary administration of the test compound on mouse liver and thyroid.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: Non-Guideline; 7-Day Mechanistic Study in Rats

Work Assignment No. 6-1-229 Y (MRID 47372520)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Building 100, Suite B
Durham, NC 27713

Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/25/09*
Secondary Reviewer: David A. McEwen, B.S.	Signature: David A. McEwen Date: *11/25/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/25/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Steven Brecher Date: *11/25/09*

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/'11

DATA EVALUATION RECORD

STUDY TYPES: 7-Day Mechanistic Study in Rats; Non-Guideline

PC CODE: 080302 **DP BARCODE:** D353273

TXR#: 0055218

TEST MATERIAL (PURITY): Fluopyram (94.7%)

SYNONYMS: *N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl) benzamide; AE C656948

CITATION: Blanck, M. (2008) Fluopyram (AE C656948): 7-day mechanistic study in the female Wistar rat by dietary administration. Bayer CropScience, Sophis Antipolis Cedex, France. Report Nos.: SA 07323, M-299274-01, ASB2008-5441, March 25, 2008. MRID 47372520. Unpublished

SPONSOR: Bayer CropScience, Alfred Nobel Str. 50, 40789 Monheim, Germany..

EXECUTIVE SUMMARY: In a non-guideline, mechanistic study (MRID 47372520), AE C656948 (94.7% a.i., Batch 08528/0002) was administered in the diet to groups of 15 female Wistar (Rj: WI [IOPS HAN]) rats/dose group at dose levels of 0 or 3000 ppm (equivalent to 0 and 193 mg/kg day) for seven days. An 80 mg/100 mL aqueous solution of bromodeoxyuridine (BrdU) was provided as drinking water during the treatment period to allow evaluation of liver cell proliferation. The rats were observed regularly for changes in mortality, clinical signs of toxicity, body weight, and food and water consumption. On the day of necropsy, the rats were exsanguinated and necropsied. Brain and liver were weighed, and duodenum and two central sections of the left and medial lobes of the liver were removed and fixed in neutral buffered 10% formalin. BrdU incorporation was determined by immunohistochemical staining, and labeling indices were calculated for the centrilobular and periportal zones. The remaining portions of the liver from 10 females from each group were taken, and microsomal preparations were made and analyzed for total cytochrome P-450 content and activities of ethoxyresorufin-O-deethylase (EROD), benzoxyresorufin-O-dealkylase (BROD), pentoxyresorufin-O-deethylase (PROD), and UDP-glucuronosyltransferase (UDPGT). The purpose of this study was to investigate the effects of the test compound on the liver, particularly hepatocellular hypertrophy and proliferation and induction of hepatic xenobiotic metabolizing enzymes.

There were no deaths or clinical signs observed in either group during treatment. Body weight and food and water consumption were similar to controls.

In the 3000 ppm females, absolute and relative (to body) liver weights were increased by 40-43%. The weight increase was associated with enlarged livers in nearly all treated females at necropsy, and diffuse centrilobular to panlobular hepatocellular hypertrophy was seen microscopically in all treated females. BrdU labeling indices were approximately 4-fold higher in treated females compared to controls. Total cytochrome P-450 content was increased by 35%, EROD activity was increased by 115%, PROD activity was increased by 329%, UDPGT activity was increased by 378%, and BROD activity was increased by 1066%.

These data demonstrated that the test compound, when administered at 3000 ppm for seven days, induced xenobiotic metabolizing enzymes in female rat liver, and caused hepatocellular hypertrophy and proliferation.

This study is considered **acceptable/non-guideline** and provides information regarding the effects of dietary administration of the test compound on rat liver.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.

EPA Reviewer: Whang Phang **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/30/11
EPA Secondary Reviewer: Myron Ottley, Ph.D. **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/11

Template version 02/06

DATA EVALUATION RECORD

STUDY TYPES: None- guideline: preliminary 28-Day Oral Toxicity Study in Rats

PC CODE: 080302 **DP BARCODE:** D353273
TXR#: 0054868

TEST MATERIAL (PURITY): AE C657188 (PCA)(99.1%) (A soil metabolite of fluopyram)

SYNONYMS: 3-chloro-5-trifluoromethylpyridine-2-carboxylic acid

CITATION: Kennel, P. (2003) AE C657188: Preliminary 28-day toxicity study in the rat by dietary administration. Bayer CropScience; Sophia Antipolis Cedex, France. Study SA 01176; M-204953-03-2. July 22, 2003. MRID 47372521. Unpublished

SPONSOR: Bayer CropScience, Alfred Nobel Str. 50, 40789 Monhein, Germany

EXECUTIVE SUMMARY: In a 28-day oral toxicity study (MRID 47372521), 5 Crl:CD(SD) IGS Br rats/sex/dose were administered AE C657188 (PCA)(99.1%) (a soil metabolite of fluopyram) at dietary concentrations of 0, 20, 200, 2000, and 20000 ppm (M: 0, 1.50, 15.0, 149, and 1574 mg/kg/day; F: 1.63, 15.9, 162, and 1581 mg/kg/day) for 28 days.

Compound-related effects on mortality, clinical signs, histopathology, clinical chemistry analyses, and urinalysis were no observed in any treatment groups. Mean body weight or food consumption were not affected in any treated male groups, but there was a slight decrease in mean body weight in 20,000 ppm females, but the decrease did not attain statistical significance (↓3% relative to the controls). Therefore, the NOAEL was 20,000 ppm (1581 mg/kg/day) (HDT).

This study is considered **acceptable/non-guideline.** It is a preliminary study to determine the potential toxic effects of this soil metabolite and to provide information for dose selection for future studies.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were presented in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: Non-Guideline; 14-Day Mechanistic Study Using Phenobarbital in Mice

Work Assignment No. 6-1-229 BB (MRID 47372522)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Building 100, Suite B
Durham, NC 27713

Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/25/09*
Secondary Reviewer: David A. McEwen, B.S.	Signature: David A. McEwen Date: *11/25/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/25/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Steven Brecher Date: *11/25/09*

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/20/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:**
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/'11

DATA EVALUATION RECORD

STUDY TYPES: 14-Day Mechanistic Study Using Phenobarbital in Mice; Non-Guideline

PC CODE: 080302 **DP BARCODE:** D353273

TXR#: 0055218

TEST MATERIAL (PURITY): Phenobarbital (99.6%)

SYNONYMS: 5-Ethyl-5-phenyl-2,4,6-(1H,3H,5H)-pyrimidinetrione

CITATION: Rouquie, D. (2008) Phenobarbital: mechanistic 14-day toxicity study in the mouse by oral gavage (hepatotoxicity and thyroid hormone investigations). Bayer CropScience, Sophis Antipolis Cedex, France. Report Nos.: SA 07326, M-299521-01, ASB2008-5445,March 31, 2008. MRID 47372522. Unpublished

SPONSOR: Bayer CropScience, Alfred Nobel Str. 50, 40789 Monheim, Germany.

EXECUTIVE SUMMARY: In a non-guideline, mechanistic study (MRID 47372522), phenobarbital (99.6% a.i., Lot/Batch 06100228) in 0.5% aqueous methylcellulose 400 was administered by daily oral gavage to groups of 15 male C57BL/6J mice/dose group at dose levels of 0 or 80 mg/kg day for either three or fourteen days. The rats were observed regularly for changes in mortality, clinical signs of toxicity, body weight, and food consumption. On the days of necropsy (Days 4 or 15), blood samples were taken from all animals for determination of TSH, T3, and T4 hormone levels. The mice were then exsanguinated and necropsied. Brain and liver were weighed, and pieces of the left and medial lobes of the liver from five mice/group were removed and fixed in neutral buffered 10% formalin. The remaining portions of the liver from these mice and the whole livers from the other ten males from each group were pooled (two whole livers pooled with one remaining portion) to generate five liver samples. Microsomal preparations were made from these five pooled samples and analyzed for total cytochrome P-450 content and activities of ethoxyresorufin-O-deethylase (EROD), benzoxyresorufin-O-dealkylase (BROD), pentoxyresorufin-O-deethylase (PROD), and UDP-glucuronosyltransferase (UDPGT).

No mortalities were observed, and there were no clinical signs of toxicity. In the 3-day exposure group, an overall mean body weight loss of 0.6 g was observed compared to a 0.3 g gain in the controls. Similarly in the 14-day exposure group, a mean body weight loss of 0.3 g was noted on Day 7 compared to a 0.4 g gain in the controls. A slight decrease in food consumption was noted in the 14-day treatment group at the beginning of treatment.

T4 levels were decreased by 27% after 3 days and by 19% after 14 days of treatment; TSH levels were increased by 9% after 14 days of treatment. No relevant changes in gross or microscopic pathology were observed in the thyroid gland.

Absolute and relative (to body) liver weights were increased by 5-23% at Days 4 and 15. The weight increases were associated with enlarged and/or dark livers observed at necropsy, and centrilobular to panlobular hepatocellular hypertrophy observed microscopically (4/5 mice at Day 4; 5/5 mice at Day 15). Additionally, an increased number of mitoses was observed in 3/5 males on Day 4. Total cytochrome P-450 content was increased by 36-146%, EROD activity was increased by 297-375%, PROD activity was increased by 1345-1381%, and BROD activity was increased by 2844-4930% on Days 4 and 15. In contrast, UDPGT activity was unaffected by treatment.

In summary, the results of this study demonstrated that phenobarbital administration (by gavage) at 80 mg/kg produced liver toxicity in male C57BL/6J mice by induction of hepatic xenobiotic metabolizing enzymes and causing gross and microscopic pathological changes in the liver. Furthermore, it had the potential to modify thyroid hormone balance by causing a decrease in T4 and a concomitant increase in TSH levels.

This study is considered **acceptable/non-guideline** and provides information regarding the effects of oral gavage administration of phenobarbital on mouse liver and thyroid.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.

DATA EVALUATION RECORD – EXECUTIVE SUMMARY

FLUOPYRAM

Study Type: Non-Guideline; 7-Day Mechanistic Study Using Phenobarbital in Rats

Work Assignment No. 6-1-229 Z (MRID 47372523)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Building 100, Suite B
Durham, NC 27713

Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/25/09*
Secondary Reviewer: David A. McEwen, B.S.	Signature: David A McEwen Date: *11/25/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Michael E Viana Date: *11/25/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Steven Brecher Date: *11/25/09*

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Whang Phang **Signature:** Whang Phang
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 6/21/11
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** Lori Brunsma
Risk Assessment Branch III, Health Effects Division (7509P) **Date:** 8/10/'11

DATA EVALUATION RECORD

STUDY TYPES: 7-Day Mechanistic Study Using Phenobarbital in Rats; Non-Guideline

PC CODE: 080302 **DP BARCODE:** D353273

TXR#: 0055218

TEST MATERIAL (PURITY): Phenobarbital (99.6%)

SYNONYMS: 5-Ethyl-5-phenyl-2,4,6-(1H,3H,5H)-pyrimidinetrione

CITATION: Blanck, M. (2008) Phenobarbital: 7-day mechanistic study in the female Wistar rat by gavage. Bayer CropScience, Sophis Antipolis Cedex, France. Report Nos.: SA 07325, M-299491-01, ASB2008-5442. March 28, 2008 MRID 47372523. Unpublished

SPONSOR: Bayer CropScience, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a non-guideline, mechanistic study (MRID 47372523), phenobarbital (99.6% a.i., Lot/Batch 06100228) in 0.5% aqueous methylcellulose 400 was administered by oral gavage to groups of 15 female Wistar (Rj: WI [IOPS HAN]) rats/dose group at dose levels of 0 or 80 mg/kg day for seven days. An 80 mg/100 mL aqueous solution of bromodeoxyuridine (BrdU) was provided as drinking water during the treatment period to allow evaluation of liver cell proliferation. The rats were observed regularly for changes in mortality, clinical signs of toxicity, body weight, and food and water consumption. On the day of necropsy, the rats were exsanguinated and necropsied. Brain and liver were weighed, and duodenum and two central sections of the left and medial lobes of the liver were removed and fixed in neutral buffered 10% formalin. BrdU incorporation was determined by immunohistochemical staining, and labeling indices were calculated for the centrilobular and periportal zones. The remaining portions of the liver from 10 females from each group were taken, and microsomal preparations were made and analyzed for total cytochrome P-450 content and activities of ethoxyresorufin-O-deethylase (EROD), benzoxyresorufin-O-dealkylase (BROD), pentoxyresorufin-O-deethylase (PROD), and UDP-glucuronosyltransferase (UDPGT). The purpose of this study was to confirm the ability of phenobarbital to induce enhanced activity of hepatic enzymes and to cause hepatocellular hypertrophy and proliferation when administered at 80 mg/kg/day for seven days.

There were no treatment-related deaths. One treated female was found dead on Day 5; however, a cause of death was not determined. All treated rats displayed reduced motor activity. Treated

rats had no mean body weight gain during treatment, while control rats gained 7 g. Food and water consumption were similar to controls.

In the treated females, absolute and relative (to body) liver weights were increased by 19-22%. The weight increase was associated with enlarged (3/14) and dark (5/14) livers observed at necropsy, and diffuse centrilobular to panlobular hepatocellular hypertrophy observed microscopically in all treated females. BrdU labeling indices were approximately 2-fold higher in treated females compared to controls, and the centrilobular labeling index was higher than the periportal labeling index. Total cytochrome P-450 content was increased by 57%, EROD activity was increased by 24%, UDPGT activity was increased by 93%, PROD activity was increased by 439%, and BROD activity was increased by 1823%.

These data demonstrated the ability of phenobarbital to induce enhanced activity of hepatic enzymes and to cause hepatocellular hypertrophy and proliferation when administered at 80 mg/kg/day for seven days.

This study is considered **acceptable/non-guideline** and provides information regarding the effects of oral gavage administration of the test compound on rat liver.

COMPLIANCE: : Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided in the report.